The Dissertation Committee for David John Del Valle II certifies that this is the approved version of the following dissertation

TOTAL SYNTHESIS OF C17-BENZENE ANSAMYCINS VIA CARBON-CARBON BOND FORMING HYDROGENATIONS

Committee:

Stephen F. Martin, Supervisor

C. Grant Willson

Guangbin Dong

Adrian T. Keatinge-Clay

Sean M. Kerwin

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by

David John Del Valle II, B.S., M.A.

Dissertation

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Dedication

To my wife Morgan and my family:

Without your love and support none of this would have been possible.

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I must first thank my family for supporting my early interests in science. Also, for instilling in me the importance of believing in myself so that I could have the confidence to overcome any challenges in my path and a strong moral compass so that could know the difference between what is easy and what is right.

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life. There is a long list of people to thank that have helped me along my way, picked me up when I fell, and provided aid to me when my situation appeared hopeless. Although I am not mentioning you by name, know I am thankful for all that you have done to help me.

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David John Del Valle II, Ph. D.

The University of Texas at Austin, 2013

Supervisor: Stephen F. Martin

Ansamycin natural products have historically been a rich source of new drugs for the treatment of bacterial infections and cancer. The C17-benzene ansamycins in particular have shown excellent preclinical results as potential anti-fungal and anti-cancer medicines. However, their thorough clinical evaluation has been hampered by the absence of a concise synthetic strategy. In order to address this issue, recently developed hydrogenative carbon-carbon bond forming methods were applied toward a short total synthesis of C17-benzene ansamycins. This class of natural products provides a challenging testing ground for these methods while facilitating the further development of compounds, which may be used as treatments for life threatening diseases.

In the first synthetic approach to the C17-benzene ansamycins key bond formations include direct iridium catalyzed carbonyl crotylation from the alcohol oxidation level followed by chelation-controlled dienylation to form the stereotriad, which is attached to the arene via Suzuki cross-coupling. The diene-containing carboxylic

acid is prepared using rhodium catalyzed acetylene-aldehyde reductive C-C coupling mediated by gaseous hydrogen. Finally, ring-closing metathesis delivers the cytotrienin core.

The second approach toward triene-containing C17-benzene ansamycins resulted in the syntheses of trienomycins A and F, which were prepared in 16 steps (longest linear sequence) and 28 total steps. The C11-C13 stereotriad was generated via enantioselective ruthenium-catalyzed alcohol CH *syn*-crotylation followed by chelation-controlled carbonyl dienylation. Finally, diene-diene ring closing metathesis to form the macrocycle. The present approach is 14 steps shorter (LLS) than the prior syntheses of trienomycins A and F, and eight steps shorter than any prior synthesis of a triene-containing C17-benzene ansamycin.

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1 BACKGROUND C17-BENZENE ANSAMYCINS

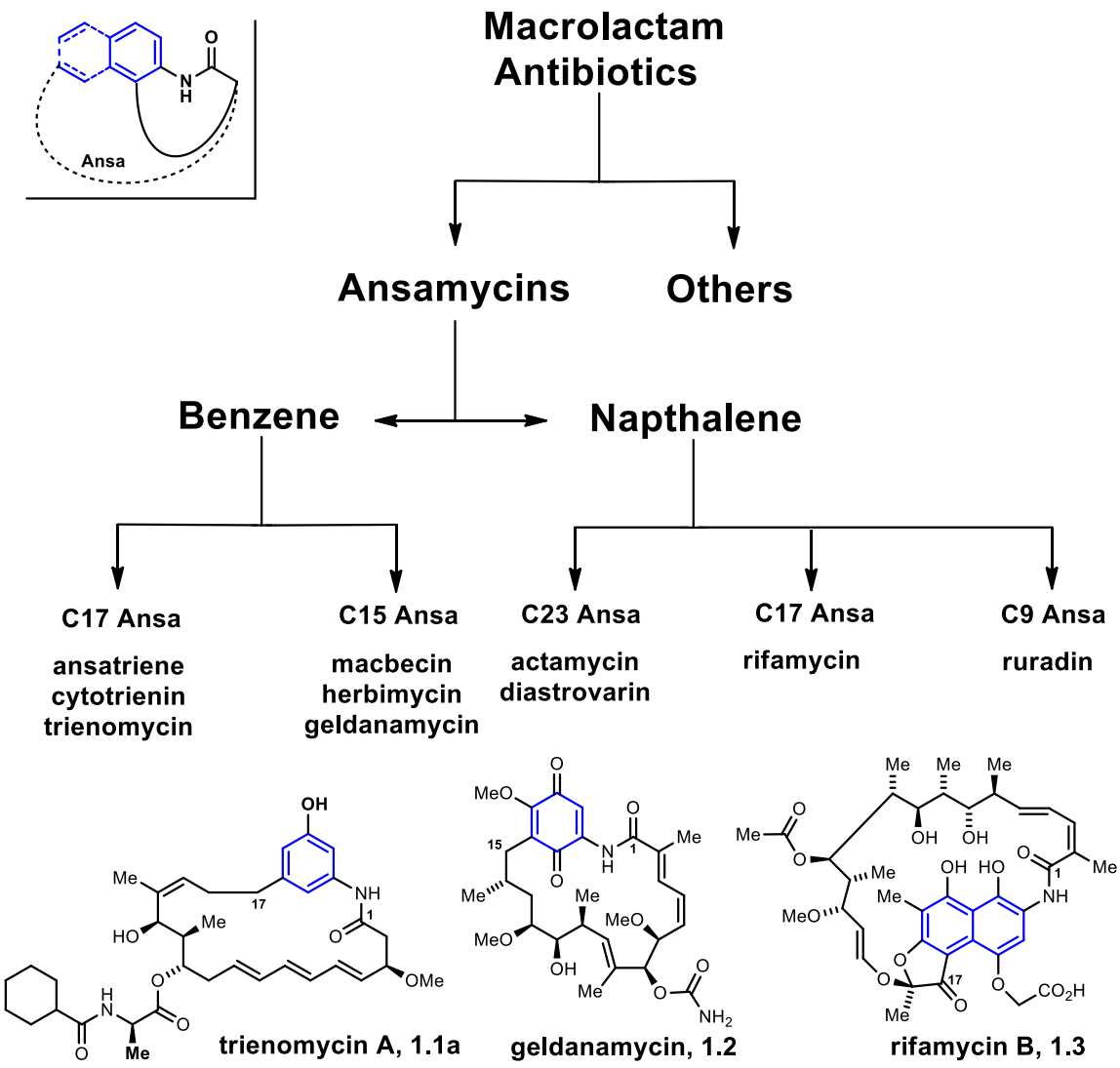
1.1 Introduction

Natural products have been a source of new medicines[1] as well as the inspiration for numerous drug discovery programs.[2] The identification and development of pharmacophores derived from natural products has led to new small molecule medicines.[3] The ability to access useful quantities of these compounds through isolation from natural sources or synthetic organic chemistry is a crucial aspect of this development process.

Roughly 20% of the top-selling small molecule drugs are polyketides isolated from soil bacteria,[3] and it is estimated that polyketides are five times more likely to possess drug activity compared to other classes of natural products.[4] Unfortunately, less than 5% of the polyketide producing soil bacteria is amenable to culture.[5] Hence, as methods to access polyketide structures through fermentation and synthesis improve, it is anticipated that polyketides will become even more important in medicine. An important polyketide subclass is the triene-containing C17-benzene ansamycins.[6] Even though this class of natural products has displayed potent anti-fungal and anti-tumor activity *in vitro*, they have received less interest from the scientific community as lead compounds. One plausible reason for the lack of development is the absence of tractable synthetic routes to synthesize analogues for a drug discovery program. The main body of this work will summarize the prior synthetic work in the area of C17-benzene ansamycin synthesis and will later describe my efforts to simplify the synthesis of this class of natural products by developing synthetic approaches that would enable analogue synthesis.

1.2 Isolation and bioactivity

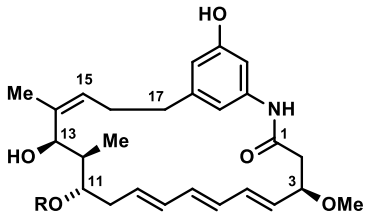
Among macrolactam antibiotics, ansamycins constitute a class of natural products characterized by a cyclic structure consisting of an aromatic moiety (naphthalene or benzene) and a polyketide chain that forms a bridge linking an aromatic moiety (Scheme 1.1). The word "ansa" is Latin for handle, and it refers to the bridging polyketide chain as a basket handle around an aromatic group.[7] The benzene and naphthalene ansamycins can be further distinguished by the length of the ansa chain. The benzene ansamycins are divided into two groups: C17 ansa chain and C15 ansa chain. Representative members of the C17- and C15-benzene ansamycins are trienomycin A (**1.1a**) and geldanamycin (**1.2**) respectively. Currently, there are several structural analogues of geldanamycin under investigation in clinical trials for the treatment of cancer.[8] Naphthalene ansamycins are divided in three groups based on ansa chain length: C23, C17, and C9 members. Several members of the napthalenoid class have exhibited potent antibiotic activity. In particular, rifamycin B (**1.3**) discovered in the late 1950's in soil samples taken from the south of France,[9] was the first ansamycin commercialized for the treatment of bacterial infections.[10]

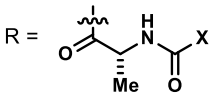


Scheme 1.1 Classification of macrolactam antibiotics

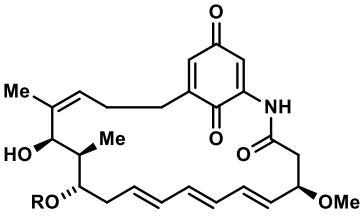
In 1967, the first C17-benzene ansamycin, mycotrienin I (**1.4a**), was isolated from a strain of *Streptomyces* by Coronelli.[11] Since then over 30 related compounds have been isolated from different *Streptomyces* and *Bacillus* strains (Figure 1.1).[6] While these compounds share the same ansa chain, it is the combination of substituents on the benzene moiety and at C11 that dictates if the compound exhibits potent or weak,

anti-fungal or anti-tumor activity. For example, mycotrienin II (**1.5a**), which contains a hydroquinone moiety and an alanine derived C11 side chain, displayed potent anti-fungal activity.[12] When the C11 side chain is absent, as shown in mycotrienin I (**1.4h**) and mycotrienol II (**1.5h**), most of the biological activity is diminished.[13] The structure of trienomycin A (**1.1a**) differs from mycotrienins I and II only at the benzene substitution.[14] Trienomycin A (**1.1a**) possesses a phenol instead of a quinone or hydroquinone, yet displays none of the anti-fungal activity seen in the mycotrienins and instead shows potent inhibitory activity on HeLa-S3 cells (ED_{50} = 128 nM).[15] In 1997, cytotrienin A-D (**1.6a-d**) were isolated, and found to possess a cyclopropyl amino acid side chain at C11.[16] Remarkably, cytotrienin A (**1.6a**) induces apoptosis in human acute promyelotic leukemia (HL-60 cells, ED_{50} = 7.7 nM). A distinct set of ansamycins, thiazinotrienomycins A-E (**1.7a-e**), were isolated in 1995 containing a benzothiazine ring system.[17] Thiazinotrienomycin E (**1.7e**) was of particular interest because it demonstrated potent activity toward a variety of human cancer cell lines.

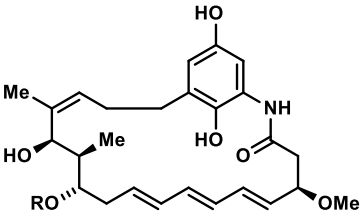




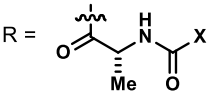
trienomycin A (X = cyclohexyl), **1.1a**
trienomycin B (X = *i*-butyl), **1.1b**
trienomycin C (X = (*S*)-*s*-butyl), **1.1c**
trienomycin D (X = cyclohexenyl), **1.1d**
trienomycin E (X = *i*-pentyl), **1.1e**
trienomycin F (X = (*E*)-2-butenyl), **1.1f**
trienomycinol, R = H, **1.1h**



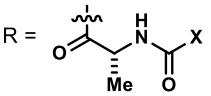
mycotrienin **I** (X = cyclohexyl), **1.4a**
mycotrienol **I**, R = H, **1.4h**



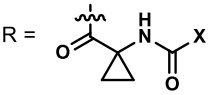
mycotrienin **II** (X = cyclohexyl), **1.5a**
mycotrienol **II**, R = H, **1.5h**

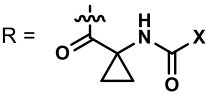


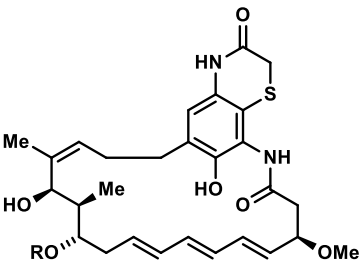
cytotrienin C (X = cyclohexenyl), **1.6c**
cytotrienin D (X = cyclohexyl), **1.6d**



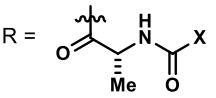
cytotrienin A (X = cyclohexenyl), **1.6a**
cytotrienin B (X = cyclohexyl), **1.6b**

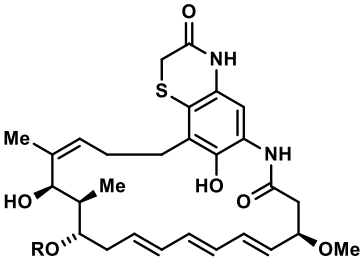






thiazinotrienomycin A (X = cyclohexenyl), **1.7a**
thiazinotrienomycin B (X = cyclohexyl), **1.7b**



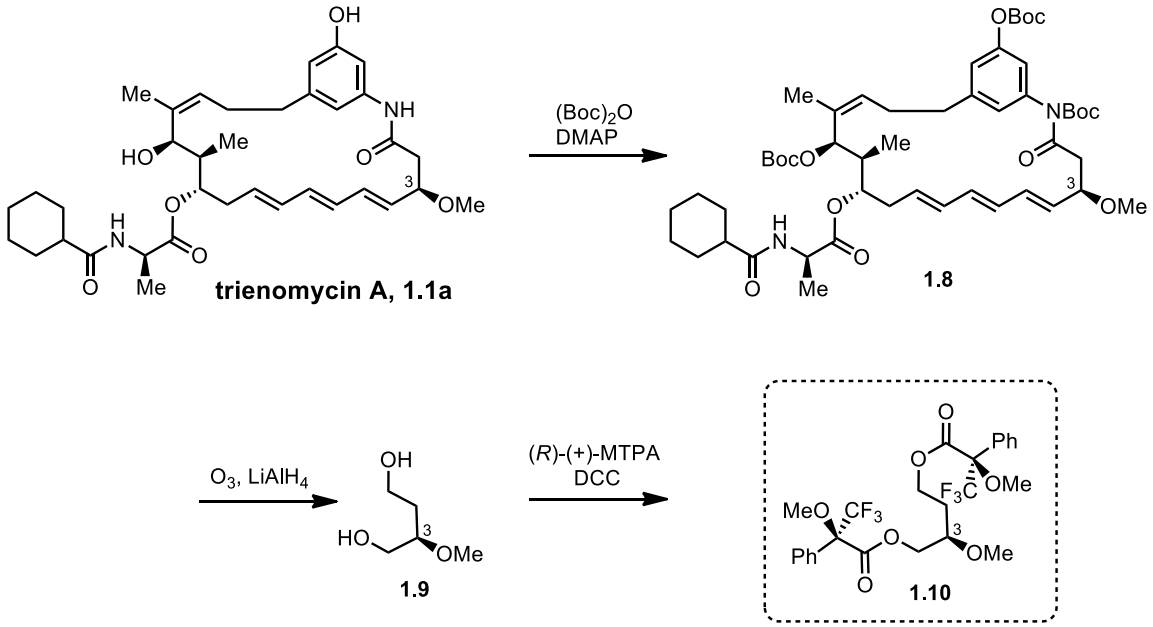


thiazinotrienomycin C (X = *i*-butyl), **1.7c**
thiazinotrienomycin D (X = cyclohexenyl), **1.7d**
thiazinotrienomycin E (X = cyclohexyl), **1.7e**
thiazinotrienomycinol, R = H, **1.7h**

Figure 1.1 C17-benzene ansamycins

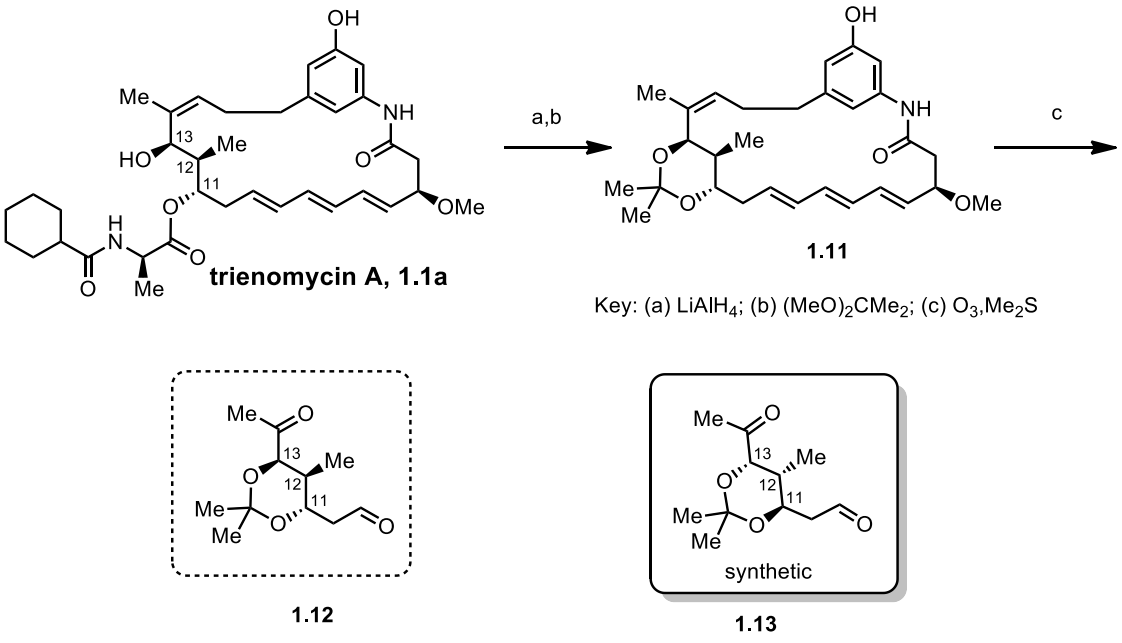
1.3 Structural elucidation

The structure of C17-benzene ansamycins were not known until the relative stereochemistry of mycotrienin I (**1.4a**) was determined using NMR experiments by Zeeck and co-workers.[18] In 1990, Smith and co-workers elucidated the absolute configuration of trienomycins A-C through degradation and independent synthesis of those degradation products.[19] Treatment of trienomycin A (**1.1a**) with an excess of $(Boc)_2O$ furnished *tris*-BOC **1.8**, subsequent reductive ozonolysis provided diol **1.9** (Scheme 1.2). Esterification of diol **1.9** provided the *bis*-Mosher ester **1.10**, which after comparison to NMR spectra of authentic samples, allowed the assignment of the stereocenter at C3 to the (*R*)-configuration.



Scheme 1.2 Degradation and elucidation of C3 stereochemistry

In order to assign the absolute configuration of the C11-C13 stereotriad, the C11 side chain of trienomycin A (**1.1a**) was cleaved with $LiAlH_4$ and subsequent acetonide protection provided intermediate **1.11** (Scheme 1.3). After an ozonolysis and dimethyl sulfide reduction, keto aldehyde **1.12** was isolated. The enantiomer of this degradation product **1.13** was obtained through an enantioselective synthesis to establish the absolute stereochemistry of keto aldehyde **1.12** as 11*S*,12*S*,13*R*. This degradation approach was also used to elucidate the structure of thiazinotrienomycin E (**1.7e**),[20] which contains the identical stereochemistry on the C1-C17 ansa chain as trienomycin A (**1.1a**). Finally, the benzene moiety of trienomycin A (**1.1a**) was oxidized with Fremey's salt to provide mycotrienin I (**1.4a**).[21] These correlation studies provided strong evidence that C17-benzene ansamycins have identical absolute stereochemistry along the ansa chain.



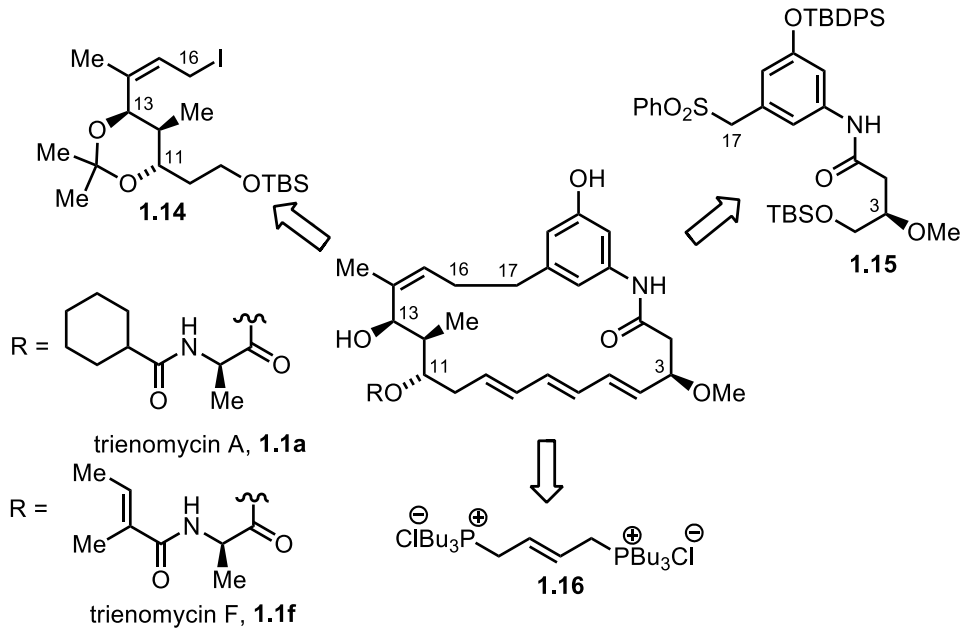
Scheme 1.3 Degradation and elucidation of C11-C13 stereochemistry

1.4 Prior total syntheses of C17-benzene ansamycins

The synthetic challenges involved with the C17-benzene ansamycins can be summarized into five major obstacles: (1) construction of the C11-C13 stereotriad, (2) the trisubstituted olefin, (3) the (*E*,*E*,*E*)-triene, (4) macrocyclization to form the 21-membered lactam, and (5) a protecting group strategy that allows access to the natural product. There have been four major syntheses of C17-benzene ansamycin published from laboratories of Smith, Panek, and Hayashi. Each major synthesis will be reviewed, focusing on how the five major obstacles were overcome.

1.4.1 SMITH'S SYNTHESIS TRIENOMYCIN A AND F

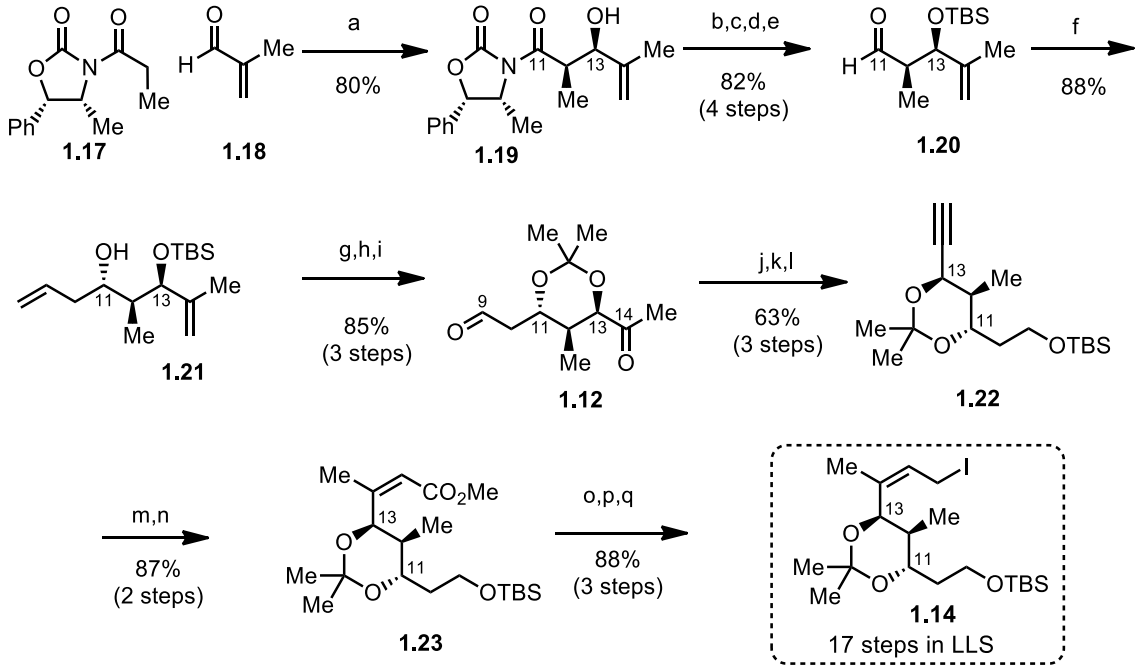
After elucidating the relative and absolute stereochemistry of trienomycin A (section 1.3), Smith and co-workers disclosed the first total synthesis of a C17-benzene ansamycin in 1995.[22] The successful synthetic strategy used an alkylation to join allylic iodide **1.14** and sulfone **1.15** (Scheme 1.4). Formation of the marocylic ring and (*E*,*E*,*E*)-triene moitey was accomplished using a *bis*-Wittig olfination with phosphonium salt **1.16**. The resulting compound provided a divergent intermediate, which was further elaborated into both trienomycin A (**1.1a**) and F (**1.1f**).



Scheme 1.4 Smith's trienomycin retrosynthesis

The forward synthesis began with an Evans aldol reaction between **1.17** and aldehyde **1.18** to furnish the desired *syn*-aldol product **1.19** (Scheme 1.5). Removal of the chiral auxiliary and conversion to aldehyde **1.20** required four steps. Construction of the C11-C13 stereotriad was completed by using the allyboration protocol developed by Brown to furnish alcohol **1.21**. Exposure of **1.21** to TBAF, followed by acetonide protection and ozonolytic cleavage afforded keto aldehyde **1.12**, which was identical to the sample obtained from degradation studies of trienomcyin A (**1.1a**). Conversion of keto aldehyde **1.12** to allylic iodide **1.14** was accomplished in three major transfomations. The first of which requried the chemoseletive reduction of keto aldehyde **1.12**, protection of the resulting alcohol as the TBS ether, and using the one-pot procedure of Negishi[23] to obtain acetylene **1.22** in three steps. Installation of the trisubsititued *Z*-olefin was

accomplished by treatment of acetylene **1.22** with *tert*-butyllithium and methylchloroformate to deliver an acetylenic ester. With the acetylenic ester in hand, conjugate addition of lithium dimethyl cuprate delivered the trisubsititued olefin **1.23**. After reduction of the methyl ester with DIBAL-H, treatment of the resulting alcohol with methanesulfonyl chloride/LiCl, and then NaI in acetone provided the unstable allylic iodide **1.14**.

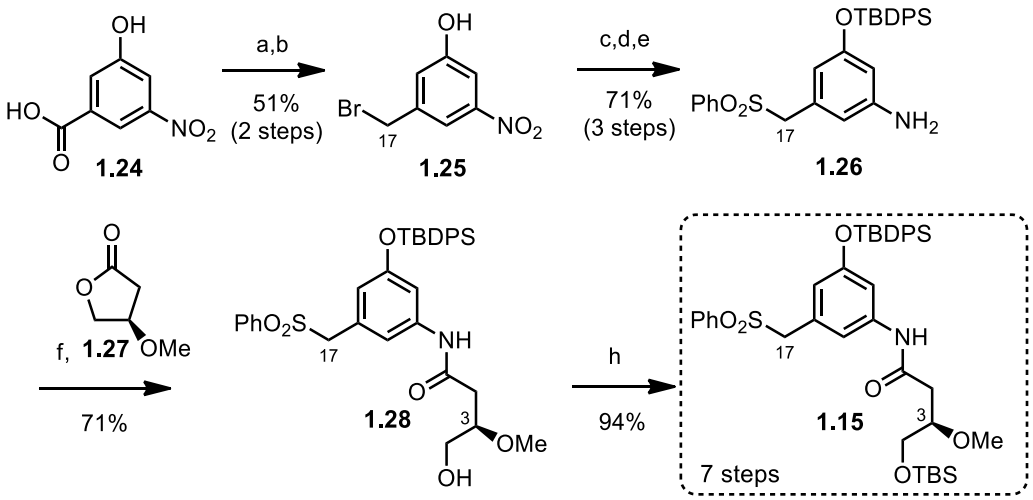


Key: (a) *n*-Bu_2BOTf, NEt_3; (b) TBSOTf; (c) LiOOH; (d) CDI, MeO(Me)NH•HCl; (e) DIBAL-H; (f) (-)-B-allyl(diisopinocampheyl)-borane; (g) TBAF; (h) $Me_2C(OMe)_2$, PTSA; (i) O_3, PPh_3; (j) $LiAl[OC(Et_3)]_3H$; (k)TBSCl; (l) NaHMDS, $ClPO(Et)_2$, *t*-BuLi; (m) *t*-BuLi, $ClCO_2Me$; (n) Me_2CuLi; (o) DIBAL-H; (p) MsCl, LiCl; (q) NaI.

Scheme 1.5 Synthesis of allylic iodide **1.14**

Preparation of sulfone **1.15** began with readily available acid **1.24**, which was subjected to borane reduction and bromination to provide bromide **1.25** (Scheme 1.6).

Displacement of the bromide, protection of the phenol as a TBDPS ether, and a catalytic reduction of the nitro group furnished aniline **1.26**. Amide bond formation with lactone **1.27** using the Weinreb protocol provided alcohol **1.28**. Protection of the alcohol as the TBS ether gave access to sulfone **1.15** in seven steps from commerically available material.

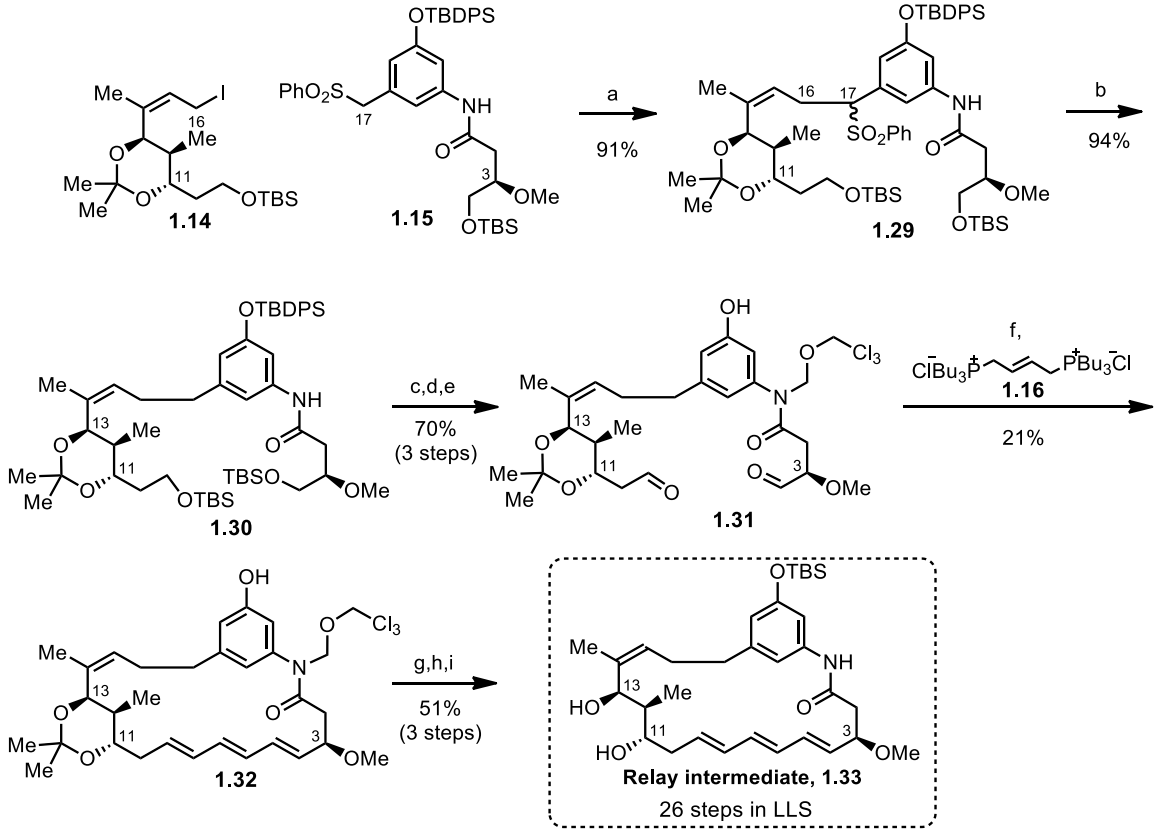


Key: (a) BH_3; (b) CBr_4, PPh_3; (c) $PhSO_2Na$; (d) TBDPSCl; (e) H_2, Pd/C; (f) $AlMe_3$, **1.27**; (h) TBSCl.

Scheme 1.6 Synthesis of sulfone **1.15**

The coupling of sulfone **1.15** and allylic iodide **1.14** furnished sulfone **1.29** as a mixture of disastereomers in 91% yield (Scheme 1.7). Desulfonylation with Na(Hg) amalgum provided amide **1.30**. The protecting group strategy for amide **1.30** proved to be critical for the *bis*-Wittig installation of the triene. Through experimentation they found that the (2,2,2-trichloromethoxy) methyl group was suitable. Exposure of amide **1.30** to KH and chloromethyl 2,2,2,-trichloroethyl ether, followed by global desilylation, and then oxidation furnished dialdehyde **1.31**. The keystone of this synthetic approach was

the macrocyclization with phosphonium salt **1.16** to install the (*E*,*E*,*E*)-triene and deliver macrocycle **1.32** in 21% yield. After three protecting group manipulations, diol **1.33** was obtained. This compound can also be accessed by semi-synthesis from trienomycin A (**1.1a**).[24]

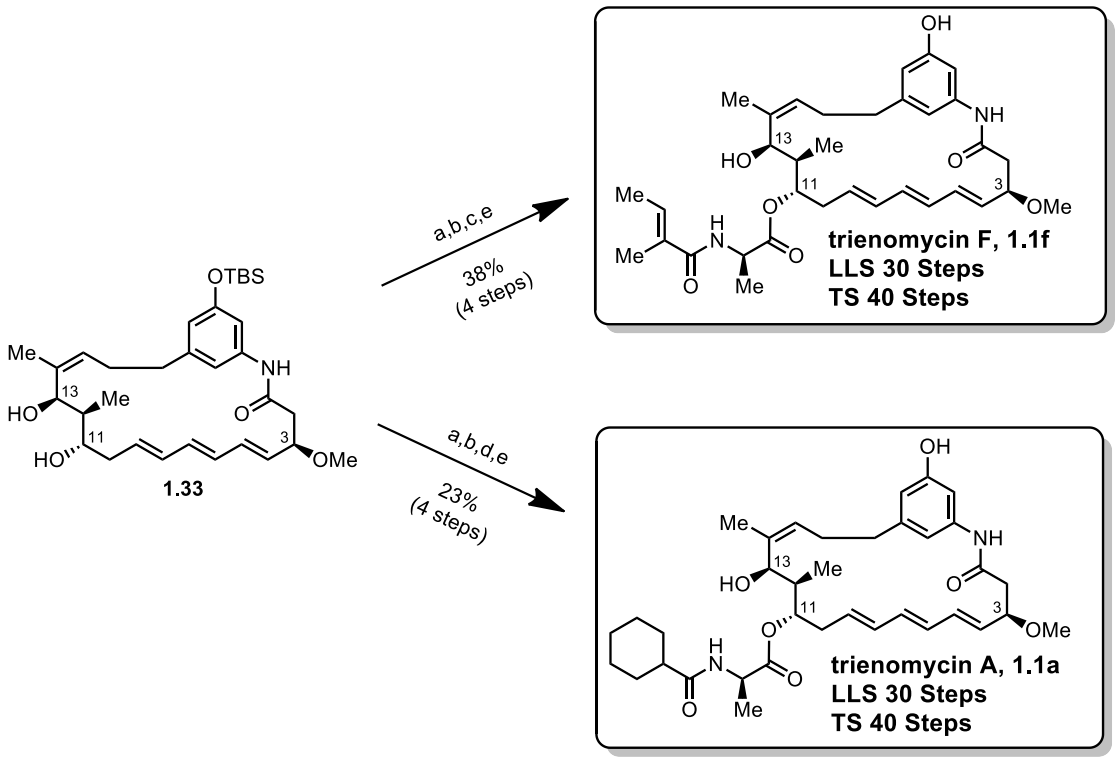


Key: (a) NaHMDS; (b) Na(Hg); (c) KH, $ClCH_2OCH_2CCl_3$; (d) TBAF; (e) Pyr•SO_3; (f) NaHMDS; (g) TBSOTf; (h) Na(Hg); (i) CSA.

Scheme 1.7 Assembly of relay intermediate **1.33**

To complete the synthesis, a flexible strategy was used starting from diol **1.33**, which was available from their degradation work. The respective side chains for trienomycin A and F were installed in a three step sequence at C11 (Scheme 1.8). The esterification was not selective and the C11/C13 regioisomers had to be separated by

HPLC. Finally, desilylation provided access to both trienomycin A and F[25], from the respective intermediates. Completion of the first total syntheses of trienomycin A and F enabled confirmation of the structures and provided a flexible strategy amenable to accessing other members of the trienomycin family.



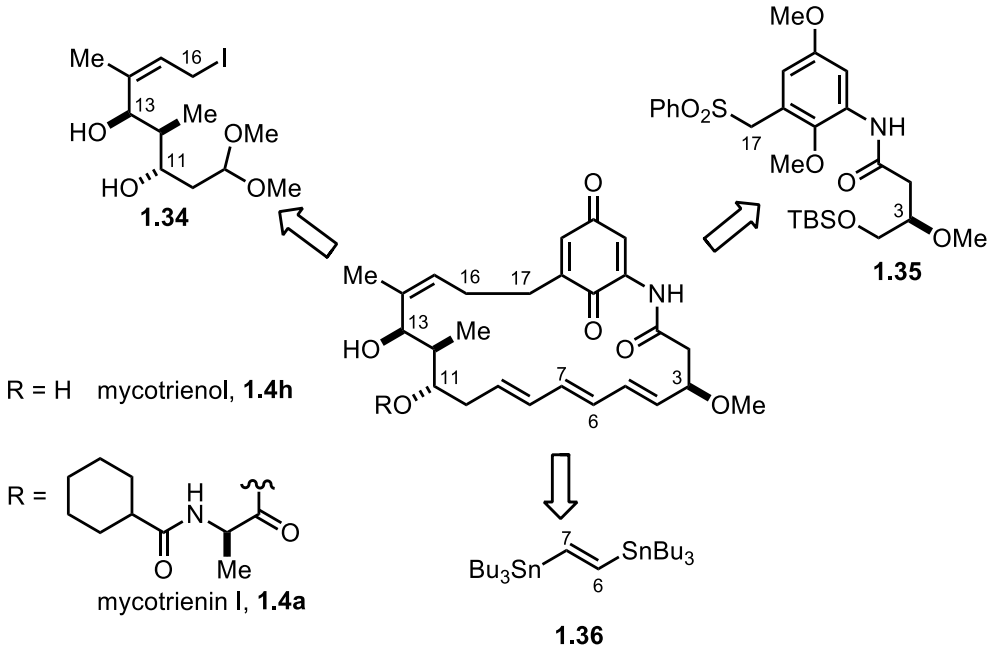
Key: (a) $(FMOC\text{-}D\text{-}Ala)_2O$, DMAP; (b) Et_2NH; (c) BOP, NEt_3, tiglic acid; (d) BOP, NEt_3, cyclohexanecarboxylic acid; (e) TBAF.

Scheme 1.8 Smith's strategy for trienomycin A and F

1.4.2 PANEK'S SYNTHESIS OF MYCOTRIENINS

Building on the strategy developed by Smith, the mycotrienins were disconnected at the C16-C17 bond to give two fragments, allylic iodide **1.34** and sulfone **1.35**, that can be joined through alkylation. The synthesis of both fragments successfully apply the

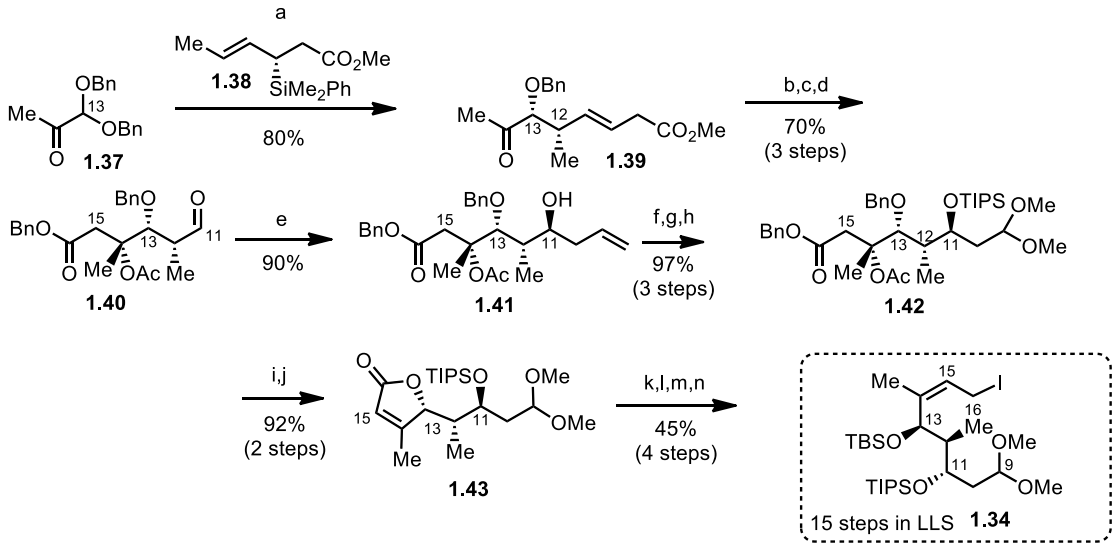
asymmetric (*E*)-crotylsilane reagents developed in Panek's laboratory.[26] The macrocyclization and (*E*,*E*,*E*)-triene formation were accomplished through the use of a stitching cross-coupling employing enedistannane **1.36**. This strategy has been successfully applied in the syntheses of rapamycin[27] and dynemycin.[28] The synthesis was completed though a common intermediate, which allowed for access to both mycotrienol (**1.4h**) and mycotrienin I (**1.4a**) (Scheme 1.9).[29]



Scheme 1.9 Panek's retrosynthesis of mycotrienin I (**1.4a**) and mycotrienol (**1.4h**)

The synthesis of allylic iodide **1.34** contains several challenges in the construction of C11-C13 stereotriad and trisubstituted (*Z*)-olefin. Treatment of keto-dibenzylacetal **1.37** and (*E*)-crotylsilane reagent **1.38** with catalytic acid furnished benzyl ether **1.39** in 80% yield and 30:1 diastereoselectivity. Exposure of benzyl ether **1.39** to the ester enolate of benzyl acetate followed by acetylation and subsequent ozonolytic cleavage

provided aldehyde **1.40** in 70% yield over three steps. Assembly of the stereotriad was completed via a chelation controlled asymmetric allylsilane addition to aldehyde **1.40** to give alcohol **1.41**. Three further synthetic operations were used to protect alcohol **1.41** as a TIPS ether and convert an alkene moiety to the dimethyl acetal **1.42**. Hydrogenation of the benzyl protecting group facilitated a spontaneous cyclization to a lactone, which after elimination of the C14 acetoxy group gave lactone **1.43**. Reductive opening of the lactone, proctection of the secondary alcohol, and conversion of the primary alcohol to an iodide provided access to intermediate **1.34** in 15 steps (LLS) from commerical material.



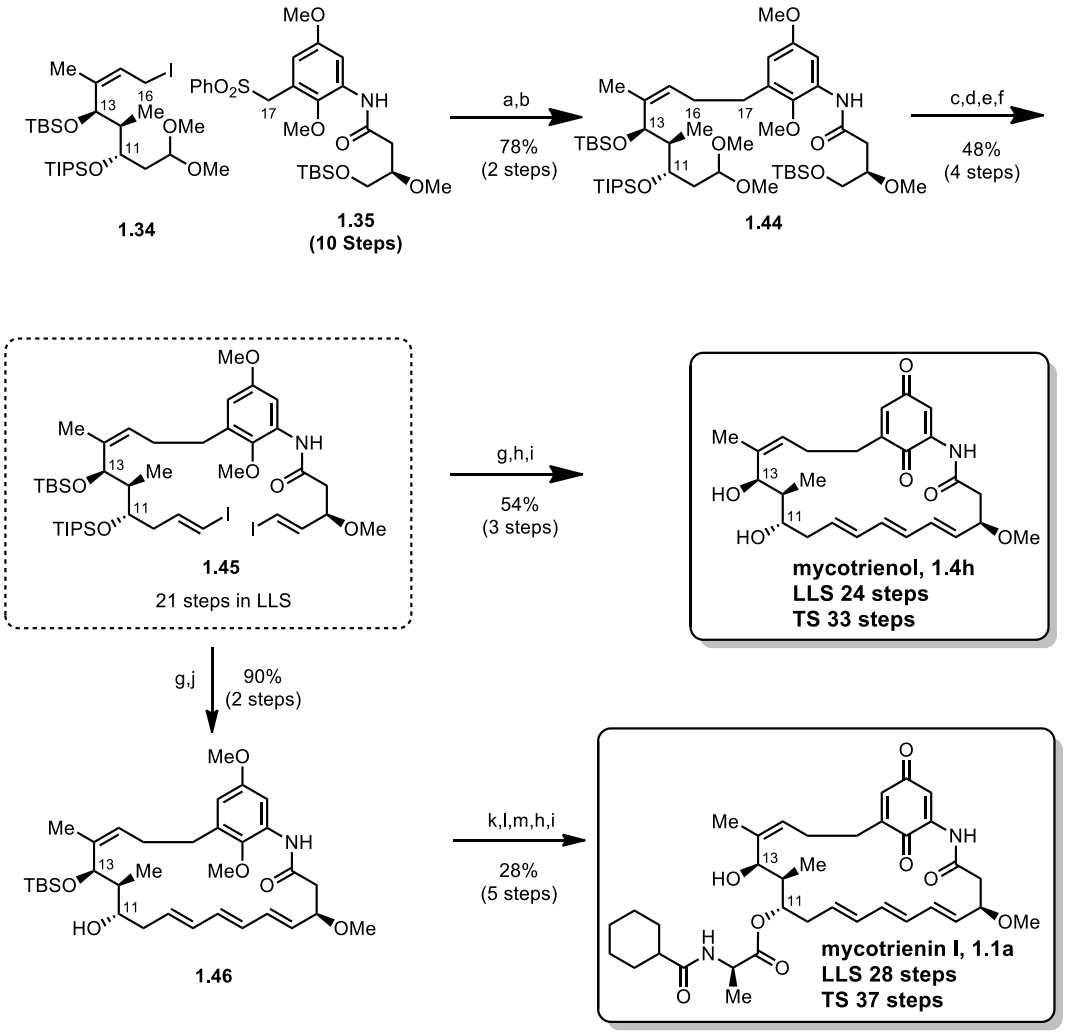
Key: (a) benzyl alcohol, PTSA; (a) cat. TMSOTf; (b) LiHMDS, benzyl acetate; (c) Ac_2O, NEt_3, DMAP; (d) O_3, Me_2S; (e) $TiCl_4$, allyltrimethylsilane; (f) TIPSOTf; (g) O_3, Me_2S; (h) MeOH; (i) H_2, Pd/C; (j) DBU; (k) $LiAlH_4$, TMEDA; (l) TBSOTf; (m) HF•Pyr; (n) $Me(PhO)_3PI$.

Scheme 1.10 Synthesis of allylic iodide **1.34**

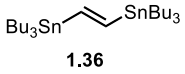
Coupling of the two major fragments was accomplished by generation of the lithium dianion of sulfone **1.35** (prepared in 10 steps) with LiHMDS to facilitate a benzylic alkylation with allylic iodide **1.34** (Scheme 1.11). Reductive desulfonylation

with Na(Hg) amalgum provided adduct **1.44**. Selective deprotections, oxidation, and homologation furnished *bis*-vinyl iodide **1.45**. From common intermediate **1.45**, both mycotrienin natural products were accessed.

The hallmark of the synthesis was a *bis*-Stille cross-coupling between enedistannane **1.36** and *bis*-vinyl iodide **1.45**, which simultaneously constructed the (*E*,*E*,*E*)-triene and induced macrocyclization. Subsequent oxidation of the aromatic moity and global deprotection furnished mycotrienol (**1.4h**) in 24 steps (LLS) from commerially available material. To complete the synthesis of mycotrienin I (**1.4a**), Panek and co-workers returned to intermediate **1.45** preformed the *bis*-Stille cross-coupling and a selective deprotection of the C11 hydroxyl group to give alcohol **1.46**. This allowed for the installation of the side chain and completion of mycotrienin I (**1.4a**) in 28 steps (LLS) from commerially available material.



Key: (a) LiHMDS; (b) Na(Hg), Na_2HPO_4; (c) HF•Pyr; (d) Pyr•SO_3, DMSO; (e) PPTS, Acetone; (f) $CrCl_2$, CHI_3; (g) $Pd(MeCN)_2Cl_2$, **1.36** (h) CAN; (i) HF; (j) MeOH, PTSA; (k) $(FMOC\text{-}D\text{-}Ala)_2O$; (l) Et_2NH; (m) BOP, NEt_3, cyclohexanecarboxylic acid;

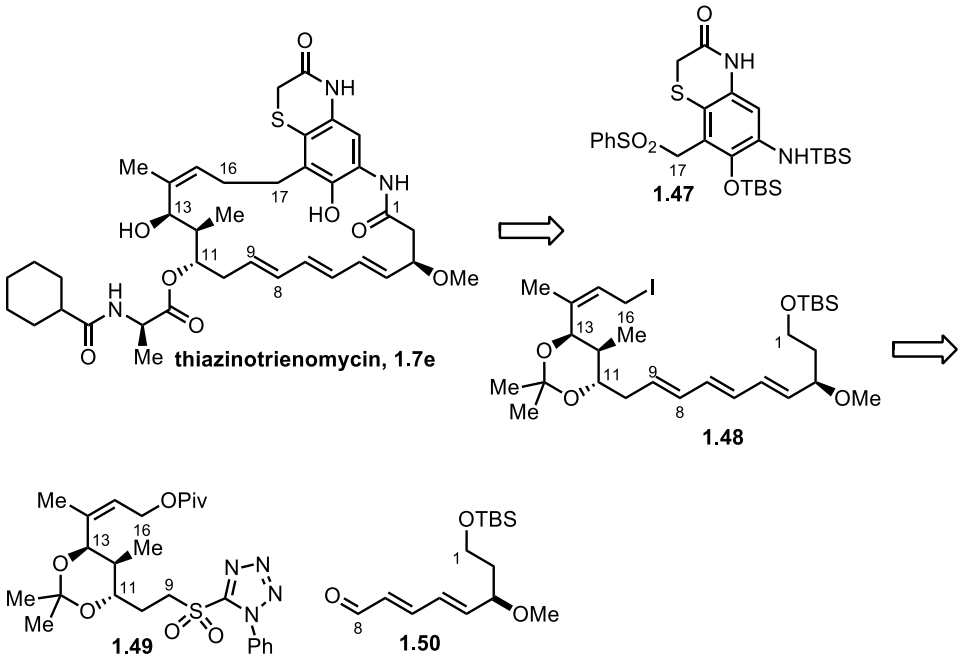


1.36

Scheme 1.11 Panek's strategy for mycotrienin I (**1.4a**) and mycotrienol (**1.4h**)

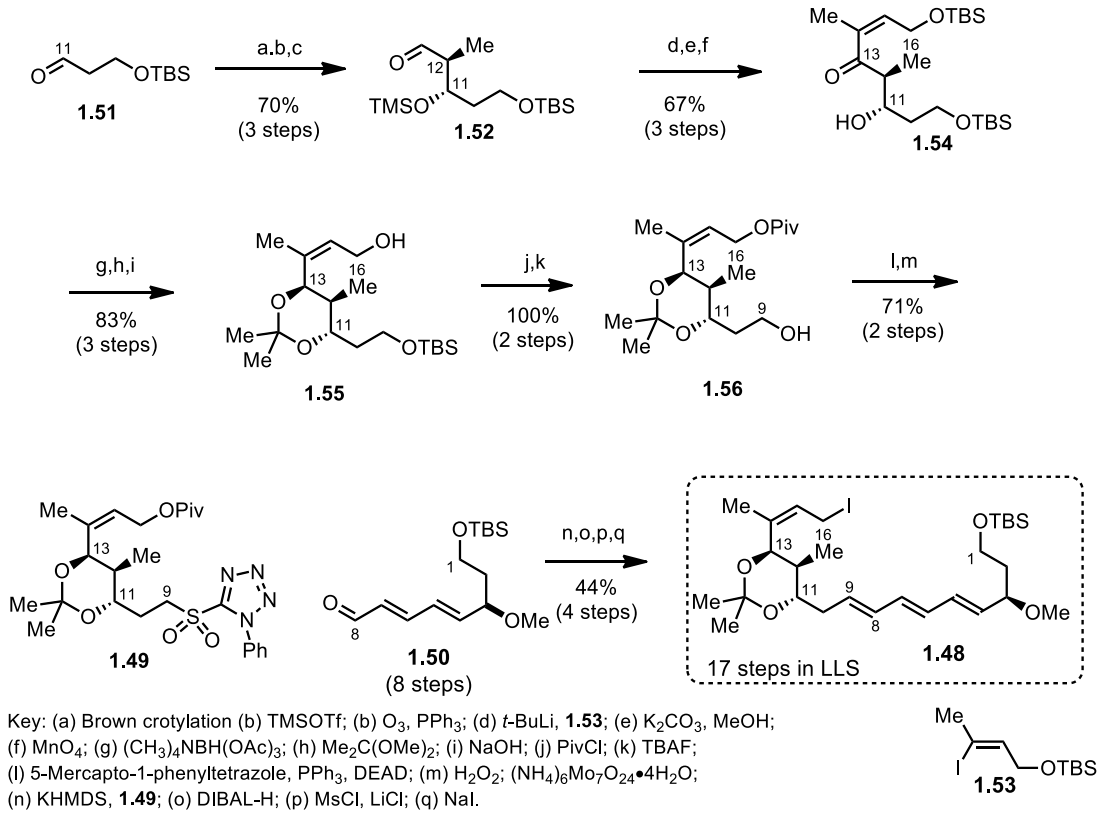
1.4.3 SMITH'S SYNTHESIS OF THIAZINOTRIENOMYCIN E

Smith and co-workers collaborated with Hosokawa and co-workers to assign the relative and absolute stereochemistry[20] of the thiazinotrienomycin E (**1.7e**) and subsequently developed a new synthetic route.[30,31] The synthesis borrowed from their earlier work on the trienenomycins and implemented several improved preparations of advanced intermediates. The C11 side chain would be installed at the end to allow flexibility in accessing other members of the family. The C16-C17 bond would arise from an alkylation of benzylic sulfone **1.47** with allylic iodide **1.48**. In a deviation from their prior work on trienomycin A and F (Scheme 1.7), the (*E*,*E*,*E*)-triene would be disconected to sulfone **1.49** and aldehyde **1.50** (Scheme 1.12).



Scheme 1.12 Smith's thiazinotrienomycin retrosynthesis

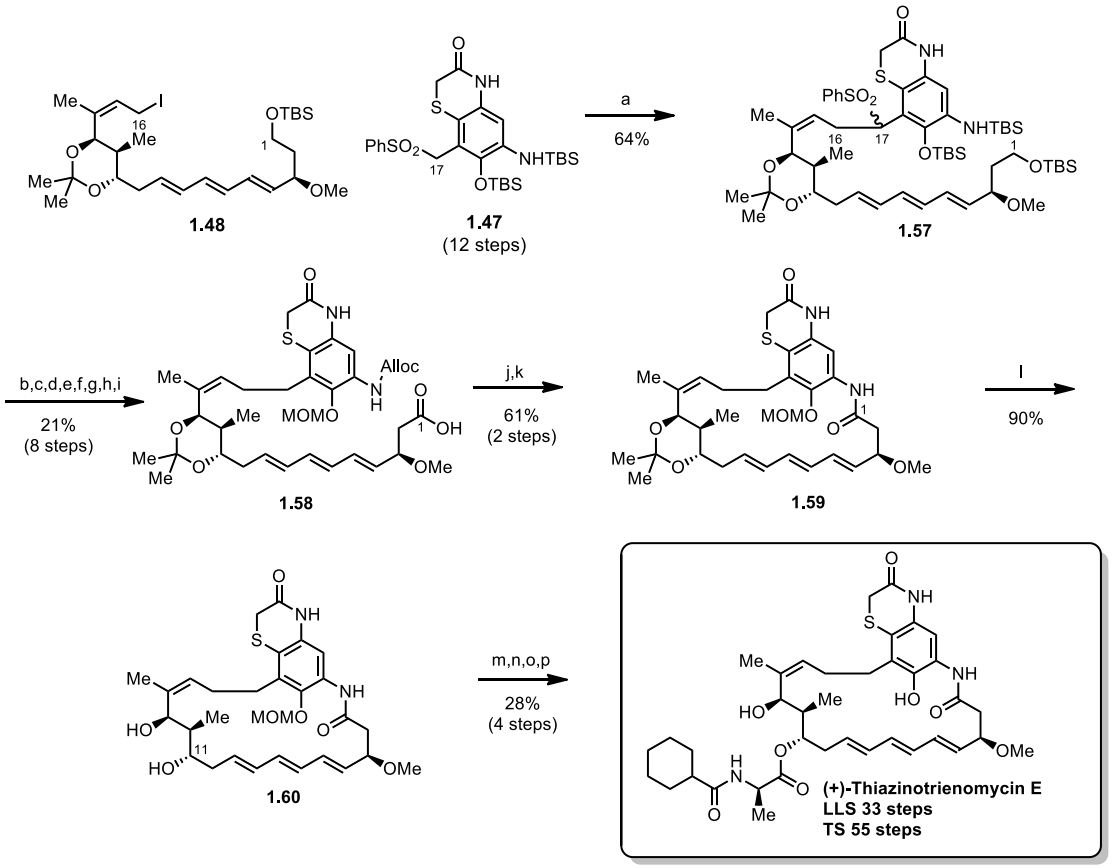
The preparation of allylic iodide **1.48** commenced with the assembly of the stereotriad utilizing aldehyde **1.51** via an *anti*-selective crotylation reagent developed by Brown (Scheme 1.13). Subsequent protection and ozonolytic cleavage furnished α-methyl aldehyde **1.52**. Lithium-halogen exchange of vinyl iodide **1.53** allowed for the alkylation of aldehyde **1.52**, which was subsequently deprotected and selectively oxidized to afford ketone **1.54**. Directed reduction with $Me_4NBH(OAc)_3$ set the C13 stereocenter, followed by acetonide protection and selective TBS deprotection provided alcohol **1.55**. A quantitative protection-deprotection sequence on alcohol **1.55** delivered alcohol **1.56**. Subsequent Mitsunobu displacement and oxidation furnished sulfone **1.49**. Construction of (*E*,*E*,*E*)-triene moiety entailed addition of aldehyde **1.50** (available in eight steps) to the anion of sulfone **1.49**. After the triene was constructed three additional operations provided access to allylic iodide **1.48**, which was obtained in 17 steps (LLS) from commerically available material.



Scheme 1.13 Synthesis of allylic iodide **1.48**

Alkylation of benzylic sulfone **1.47** (available in 12 steps) with allylic iodide **1.48** provided triene **1.57** in 64% yield as a mixture of diastereomers (Scheme 1.14). An eight step sequence commencing with a reductive desulfuration followed by a series of protecting group manipulations and oxidations was used to access acid **1.58**. From acid **1.58**, a two step precedure was developed to deprotect the aniline and form the macrocylic with Mukaiyama's salt to give macrolactam **1.59**. A selective cleavage of the C11-C13 acetonide furnished diol **1.60**. To finish the synthesis and confirm the structure of the thiazinotrienomycins, the same three step protocol to install the C11 side chain used in the trienomycins and mycotrienins was employed. Finally, cleavage of the MOM

ether with 3 N HCl furnished thiazinotrienomycin E (**1.7e**) in 33 steps (LLS) from commerically available material.



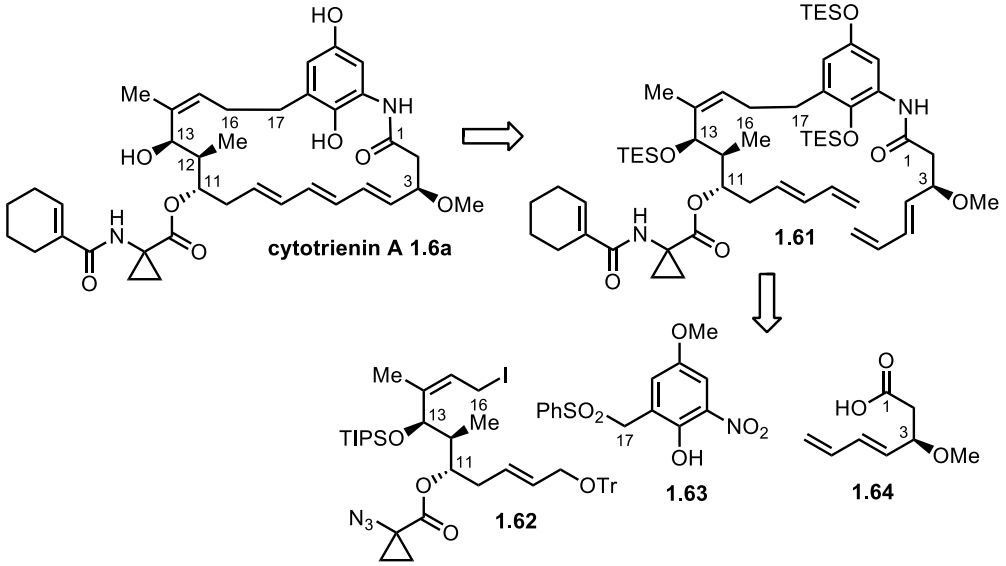
Key: (a) NaHMDS; (b) Na(Hg); (c) SiO_2, $CHCl_3$; (d) AllocCl; (e) TBAF-HOAc; (f) MOMCl; (g) TBAF; (h) $Py{\bullet}SO_3$; (i) $NaClO_2$; (j) $Pd(PPh_3)_4$, Dimedone; (k) Mukaiyama Salt, NEt_3; (l) CSA; (m) $(FMOC\text{-}D\text{-}Ala)_2O$, DMAP; (n) Et_2NH; (o) BOP, NEt_3, cyclohexanecarboxylic acid; (p) 3N HCl.

Scheme 1.14 Smith's strategy for thiazinotrienomycin E (**1.7e**)

1.4.4 HAYASHI'S SYNTHESIS CYTOTRIENIN A

In 2008, Hayashi and co-workers,[32] reported a total-synthesis of cytotrienin A (**1.6a**). They sought to construct the triene through a diene-diene ring closing metathesis (RCM), which required the synthesis of bis(diene) **1.61** (Scheme 1.15). Proof of concept studies had been reported by Panek,[33] validating the

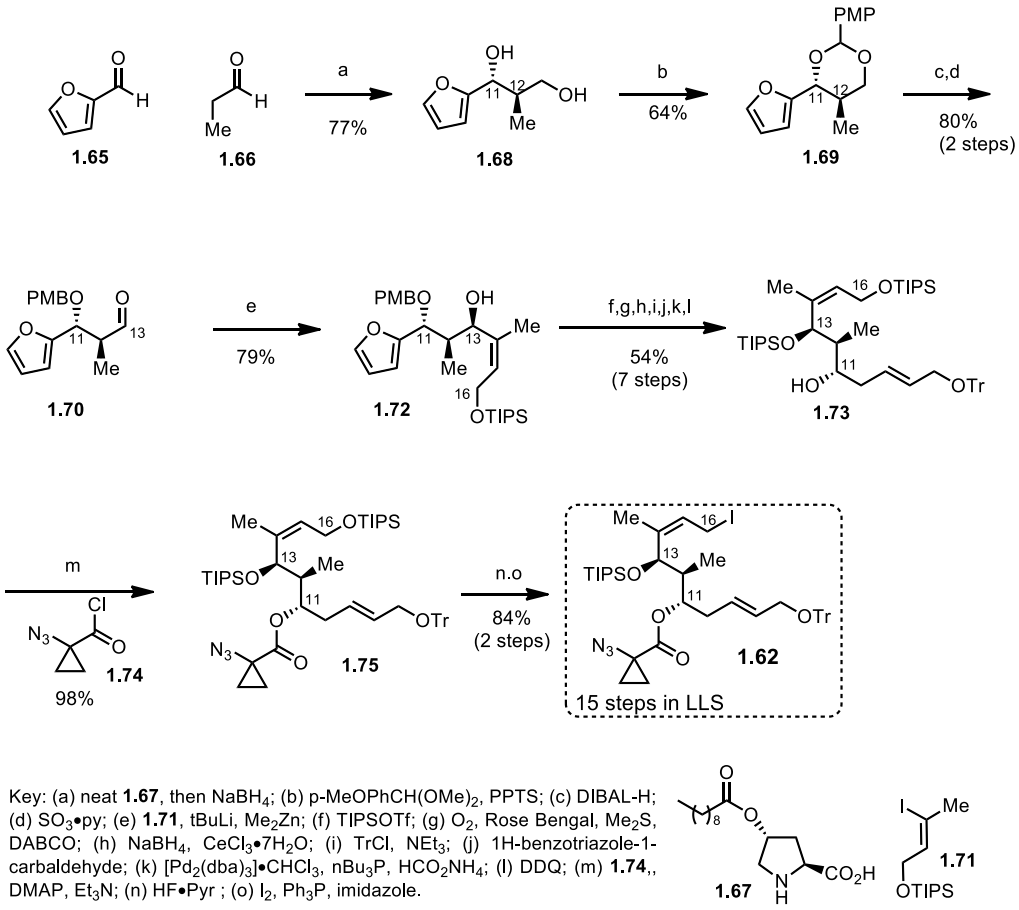
feasablity of a diene-diene RCM to furnish the (*E*,*E*,*E*)-triene. Futher disconnection at the C16-C17 bond and C1 amide bond required three major fragments: allylic iodide **1.62**, benzylic sulfone **1.63**, and dienoic acid **1.64**. Noteworthy in their work was the use of proline catalysis to construct the C11,C12, and C3 stereocenters.



Scheme 1.15 Hayashi's retrosynthesis of cytotrienin A (**1.6a**)

Initial attempts of a large scale organocatalyzed aldol between aldehyde **1.65** and propanal **1**.**66** were found to be problematic (Scheme 1.16). By conducting the reaction without solvent and using a modified proline cataylst **1.67**, the desired diol **1.68** was obtained in good yield and selectivity. Diol **1.68** was protected as PMP acetal **1.69**, reduced with DIBAL-H to afford an alcohol, and oxidized to furnish aldehyde **1.70**. Exposure of aldehyde **1.70** to a vinylzincate,[34] prepared from vinyl iodide **1.71** with *t*-BuLi and Me_2Zn delivered stereotriad **1.72** in good yield and selectivity. Remarkably, Hayashi and co-workers were able to construct the C11-C16 fragment containing the

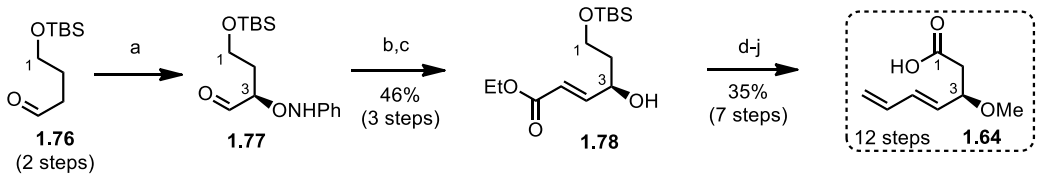
stereotraid and (*Z*)-trisubsituted olefin in just five steps. In order to elaborate stereotriad **1.72** into a tractable synthentic intermediate an additional seven steps were needed to obtain alcohol **1.73**. Esterification with acid chloride **1.74** furnished intermediate **1.75**, which after two additional steps, provided access to allylic iodide **1.62** in 15 steps (LLS) from commerical material.



Scheme 1.16 Synthesis of allylic iodide **1.62**

Acid **1.64** was synthesized via proline catalyzed α-aminoxylation of aldehyde **1.76** to provide an unstable intermediate **1.77**. The crude mixture was immediately

subjected to an olefination and treated with $CuSO_4$/MeOH to afford alcohol **1.78** in 46% yield over three steps. A seven step sequence was necessary to methylate the C3 hydroxyl group, install the diene, and oxidize the C1 hydroxyl group to carboxylic acid. Thereby completeting to synthesis of the major fragment acid **1.64** in 12 steps from commerically available material (Scheme 1.17).

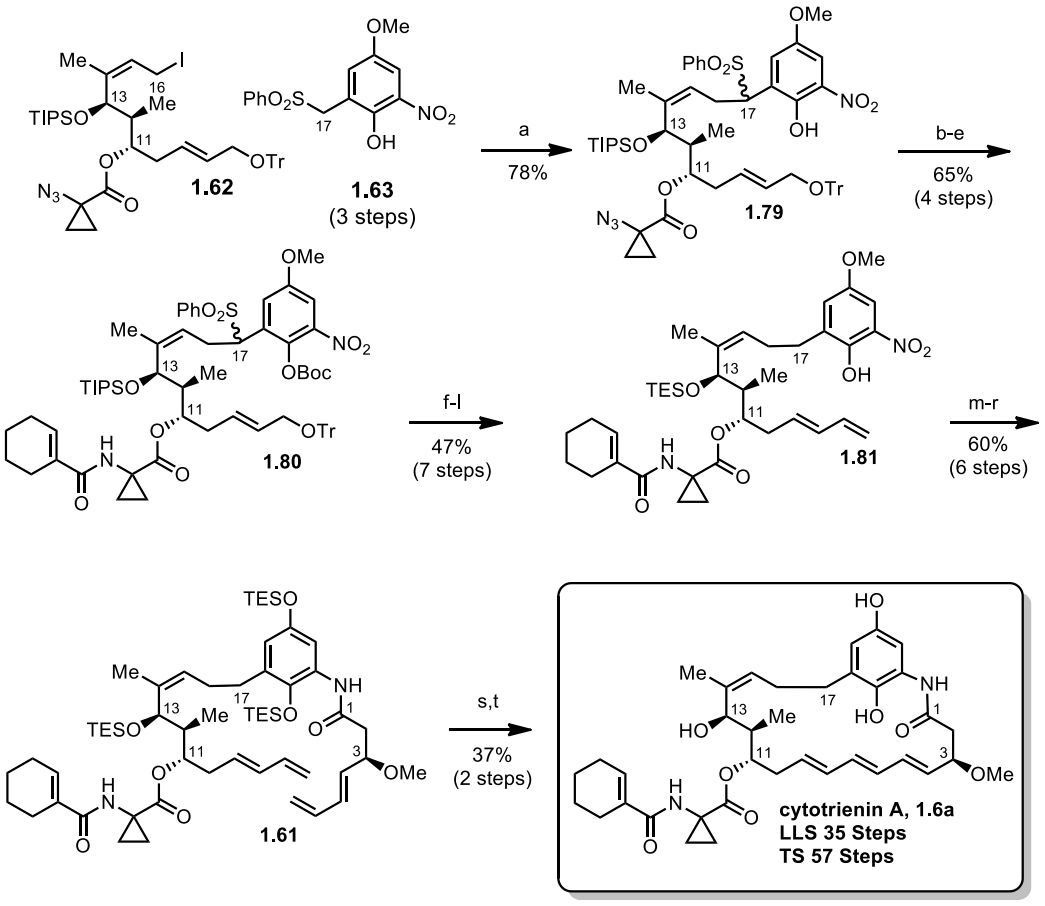


Key: (a) nitrosobenzene, L-proline; (b) triethyl phosphonoacetate, NaH; (c) $CuSO_4$; (d) MeI, NaH; (e) DIBAL-H; (f) MnO_2; (g) $[Ph_3PCH_3]I$, tBuOK; (h) py(HF); (i) SO_3•py; (j) $NaClO_2$.

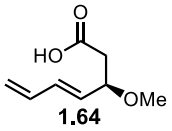
Scheme 1.17 Hayashi's synthesis of acid **1.64**

Construction of the C16-C17 bond by alkylation of the lithium dianion of sulfone **1.63** with allylic iodide **1.62** gave fragment **1.79** in 78% yield as a mixture of diastereomers (Scheme 1.18). Elaboration of the C11 side chain required selective azide reduction without affecting the nitro group. This was accomplished in four steps to provide advanced sulfone **1.80**. The chemoselective reduction of the C17 sulfone in the presence of the nitro group proved to be difficult as well. Thus, seven steps were necessary to accomplish the sulfone reduction, construction of the diene, and several protecting group manipulations to deliver diene **1.81**. From diene **1.81** reduction of the nitro group, coupling of acid **1.64**, and protecting group adjustments provided a globally TES protected bis(diene) **1.61** in six steps. In order to cleave the protecting groups in the final steps, it was important to have a TES ether at C13, as the TIPS ether at C13 could

not be removed after the RCM. Finally, conclusion of the synthesis with a diene-diene RCM and deprotection of the TES ethers delivered cytotrienin A (**1.6a**) in 35 steps (LLS) from commerially available material.



Key: (a) LiHMDS; (b) $(Boc)_2O$, DMAP; (c) 1,3-propanedithiol; (d) 1-cyclohexenecarboxylic acid, EDCI, DMAP; (e) pyrrolidine; (f) $NaBH_4$; (g) AllocCl, Et_3N; (h) $TsOH•H_2O$, MeOH; (i) MnO_2; (j) $[Ph_3PCH_3]I$, *t*-BuOK; (k) HF; (l) TESOTf, iPr_2EtN; (m) $NaBH_4$, S_8; (n) **1.64**, BOP-Cl, iPr_2EtN; (o) K_2CO_3, MeOH; (p) MnO_2; (q) $NaBH_4$; (r) 4-triethylsiloxy-3-penten-2-one; (s) Grubbs I catalyst; (t) Amberlyst 15



Scheme 1.18 Hayashi's strategy for cytotrienin A (**1.6a**)

1.5 Conclusions

The potent anti-fungal and anti-cancer activity of C17-benzene ansamycins compelled researchers to learn more about their structure, biological target, and synthetic approaches. Each of the completed syntheses confirmed the proposed structure and improved methodologies used to construct these complex natural products. However, those routes were not efficient and were unable to modify the structures as needed for a drug discovery program. Our intention was to develop a shorter and more versatile synthetic route that combines the best chemistry of the previous syntheses with our newly developed metal-catalyzed transformations. In doing so, this would develop a synthetic route that uses roughly half of the steps as the previous syntheses, thereby enabling future drug discovery efforts.

2 CARBON-CARBON BOND FORMING HYDROGENATIONS

2.1 Introduction and scope

One of the most significant challenges facing the field of synthetic organic chemistry is the development of more efficient protocols for known transformations. The reduction of the number of steps required for a given target is a metric for improvement that has received extra attention from the scientific community.[35] Another measurement is atom efficiency,[36] which takes into account some of the pre-activation required to access the starting materials for a reaction and the amount of stoichiometric waste created from a reaction. An ideal reaction would be one wherein all of the reagents react together to produce a single more complex product without any waste generation.[37] The prototypical examples of such reactions are hydrogenation and alkene hydroformylation (Figure 2.1). In hydrogenation, hydrogen is added across an olefin to produce a single product without the generation of waste by-products. In hydroformylation, an olefin is hydrogenated with carbon monoxide to furnish the product of reductive C-C bond formation. In contrast to conventional hydrogenation where hydrogen is added across a single functional group, the elements of molecular hydrogen were added over two functional groups coupled with C-C bond formation. The expansion of this concept in the laboratory of Professor Michael Krische has led to a generalized process wherein the hydrogenation of unsaturated moieties with diverse imine or carbonyl compounds delivers products of C-C coupling. A direct result of this research has been the development of hydrogen-mediated variants of classical organometallic transformations.

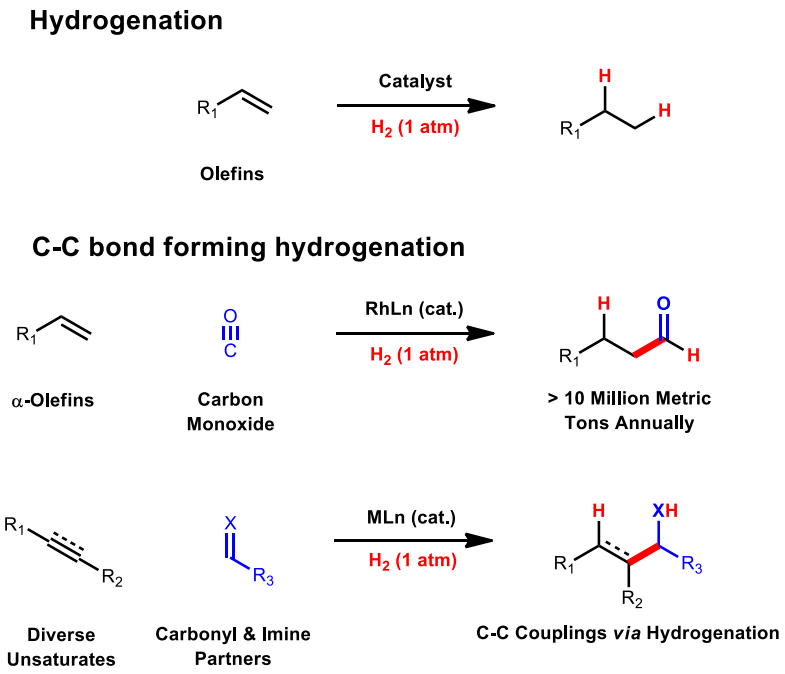


Figure 2.1 Atom economical transformations

In classical methods for the construction of allylic and homo-allylic alcohols, organometallic reagents are used to facilitate the stereoselective addition to carbonyl compounds (Figure 2.2). These reagents require pre-activation and generate stoichiometric amounts of metal waste. An alternative to these transformations would be to employ a C-C bond forming hydrogenation allowing the construction of those motifs with less pre-activation and waste.

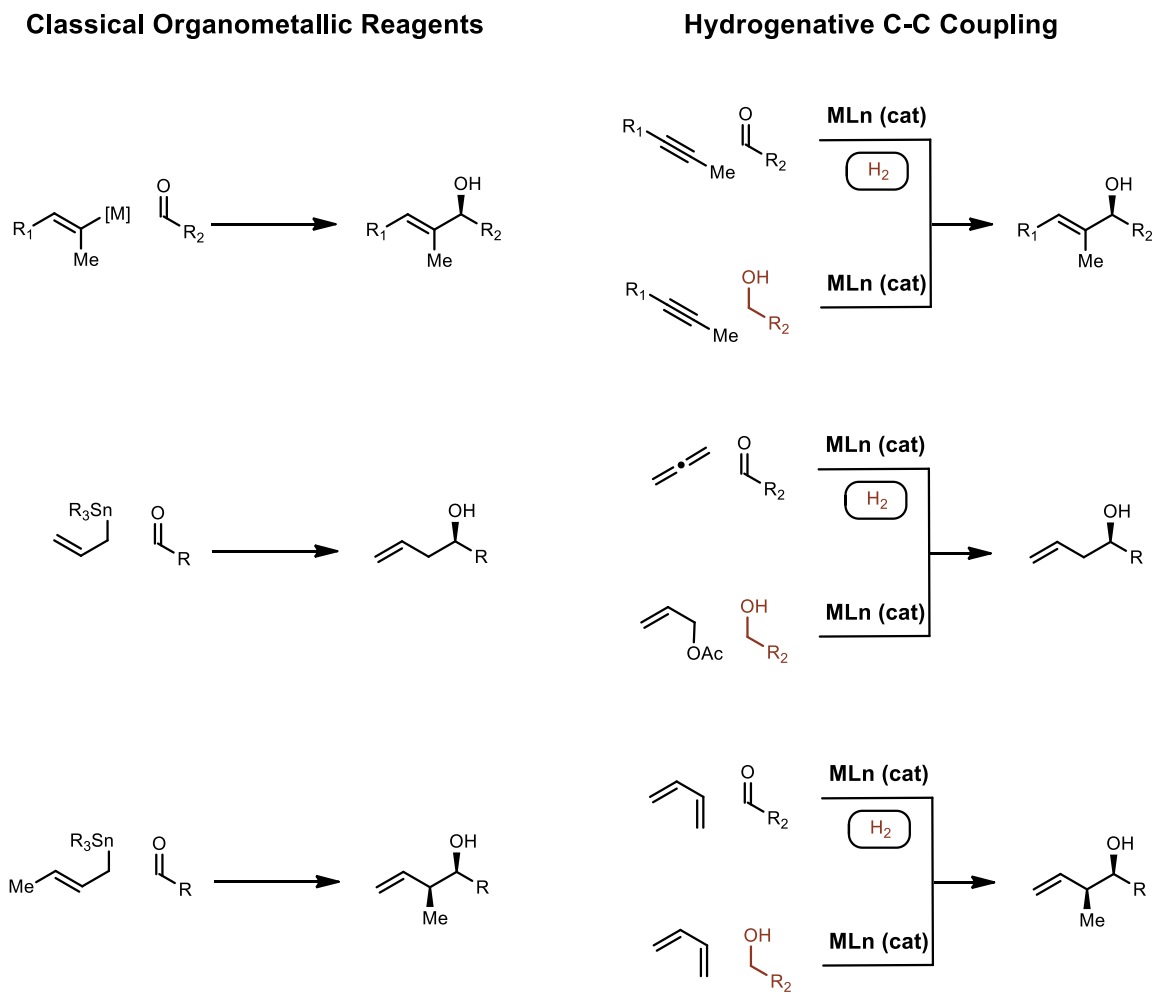


Figure 2.2 Hydrogenative C-C coupling as an alternative to classical organometallic reagents

In an effort to provide context, a brief overview of classical methods for enantioselective construction of allylic and homo-allylic alcohols through carbonyl vinylation, allylation, and crotylation will be discussed. Subsequently, alternative transformations using hydrogenative C-C bond forming reactions that are relevant to this

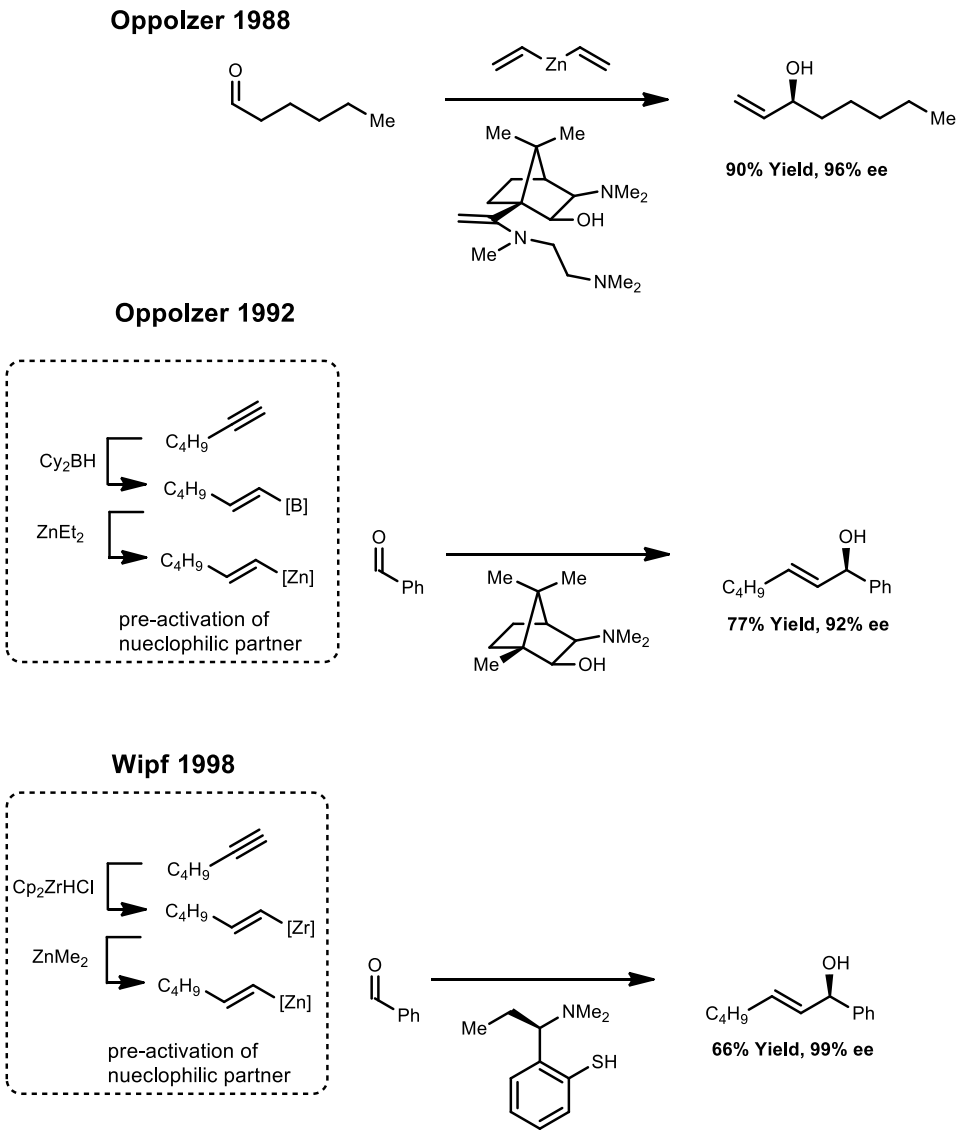
body of work will be presented. Finally, contributions to the development of a two-directional asymmetric carbonyl allylation reaction are also shown.

2.2 Catalytic enantioselective carbonyl vinylation reactions

2.2.1 STOICHIOMETRIC ORGANOMETALLIC APPROACHES

2.2.1.1 Vinylzinc approaches

In 1988, Oppolzer reported the first catalytic asymmetric addition of divinylzinc to aliphatic aldehydes providing chiral allylic alcohols in high yield and selectivity (Scheme 2.1).[38] That seminal work was followed by a modification of the protocol where an alkyne was hydroborated to furnish a vinylborane, which was then transmetallated with dimethylzinc. The resulting vinylzinc reagent participated in a catalyzed addition to an aldehyde. The transmetallation approach proved to be an effective method for the construction of allylic alcohols,[39] and was employed in the synthesis of (*R*)-(-)-muscone.[40] An additional modification of this strategy was reported by Wipf, which employed a vinylzirconocene to access the vinylzinc reagent. [41,42] Although these strategies have been broadly utilized in several applications,[43] the drawback is that they require multiple equivalents of organometallic reagents for the pre-activation of the nucleophilic partner to make a single C-C bond. This is problematic if the protocols are used on a very large scale; the excess of metal reagents lead to undesirable and costly amounts of waste.

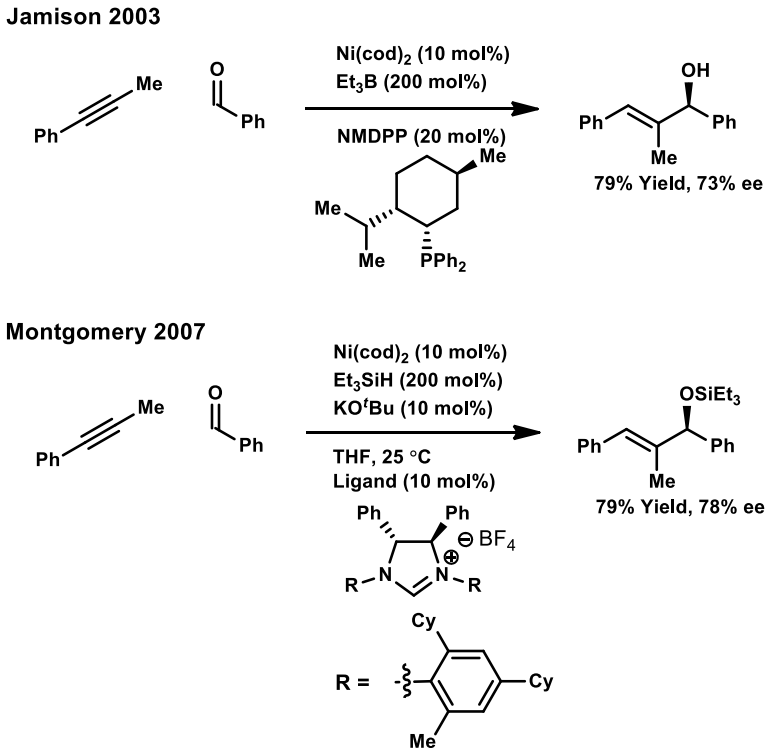


Scheme 2.1 Enantioselective vinylzinc additions

2.2.1.2 Direct alkyne approaches

Pioneering work by Ojima[44] and Montgomery[45] demonstrated the feasibility of a direct coupling of alkynes to aldehydes using nickel catalysis and a stoichiometric reluctant. Later, Jamison and co-workers[46] reported the enantioselective coupling of

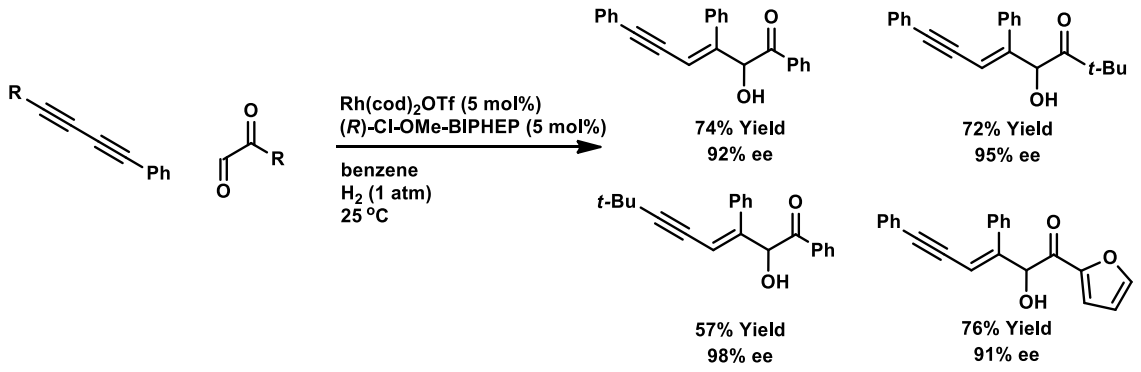
alkynes with aldehydes to furnish chiral allylic alcohols without the need for pre-activation of the nucleophilic partner (Scheme 2.2). This major advancement in catalytic enantioselective vinylation was followed by a report from Montgomery[47] that employed a non-metallic reductant and a chiral N-heterocyclic carbene ligand. Although the pre-activation component was removed, the atom economy of this transformation could be further improved by using hydrogen as the terminal reductant.



Scheme 2.2 Enantioselective coupling of alkynes to aldehydes

2.2.2 RHODIUM-CATALYZED ENANTIOSELECTIVE HYDROGENATIVE VINYLATIONS OF ALDEHYDES

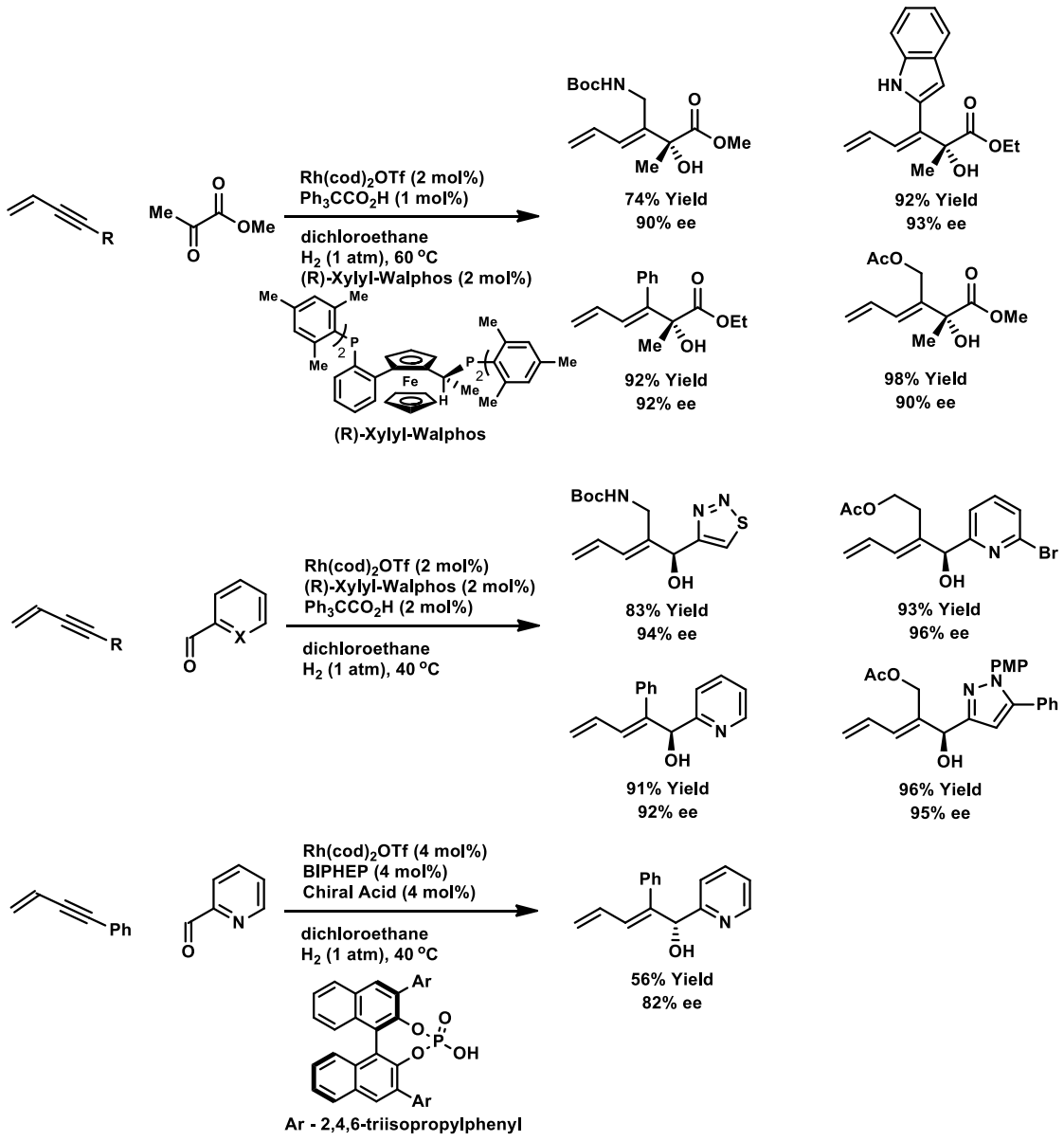
Initial success by Krische and co-workers with the hydrogenative coupling of unsaturated systems to aldehydes and ketones demonstrated the importance of employing cationic metals in C-C bond forming hydrogenation.[48] By employing a chirally modified cationic rhodium catalyst they reported the first enantioselective hydrogenative coupling of 1,3-diynes to various glyoxals to furnish optically enriched α-hydroxy ketones as achieved (Scheme 2.3).[49] With this promising preliminary result, further investigations were conducted to expand the scope of unsaturates beyond diynes.



Scheme 2.3 Coupling of 1,3-diynes to glyoxals

In 2006, the importance of a Brønsted acid additive was realized in the coupling of conjugated alkynes and α-ketoesters to furnish products of carbonyl addition (Scheme 2.4).[50] Different enynes and α-ketoesters were used to explore the reaction scope, thus demonstrating uniformly high yields and selectivity across a range of substrates. Further investigation of the acid additive expanded the substrate scope to

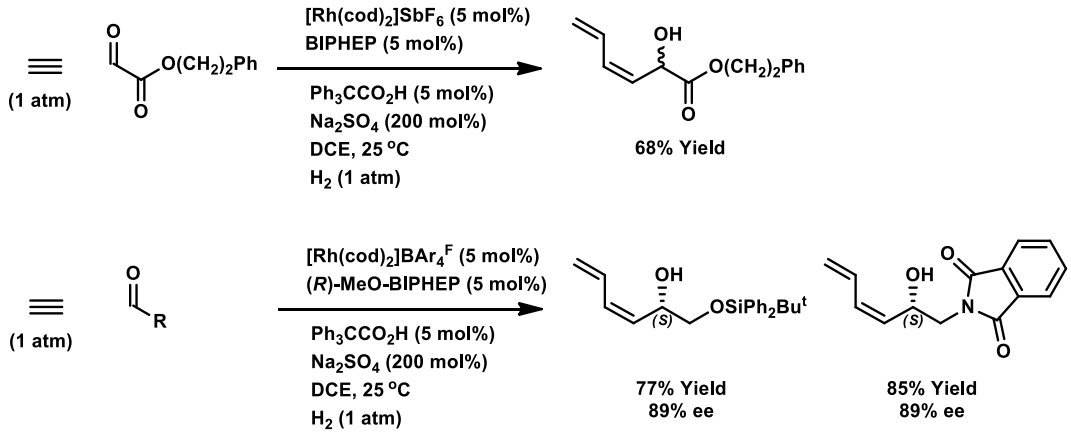
include heteroaromatic aldehydes and ketones (Scheme 2.4).[51] Subsequent studies showed the combination of a chiral phosphoric acid and an achiral ligand can also provide the indicated product. The effect the chiral acid resulted in lower yield and selectivity compared to using chiral ligands. Further experimentation with pyruvates and glyoxalates, suggested that protonation of the heterocyclic moiety is responsible for asymmetric induction.



Scheme 2.4 Hydrogenative coupling of enynes

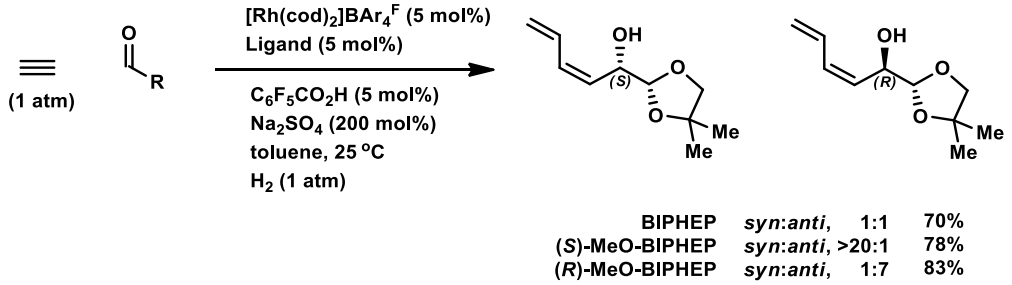
Despite extensive optimization, the reaction scope was still limited to conjugated alkynes and activated aldehydes. However, it was reported that by using a cationic rhodium catalyst a mixture of acetylene and hydrogen gas, aldehydes could undergo

hydrogenative coupling to furnish products of *Z*-butadienylation (Scheme 2.5).[52] When a chiral ligand was employed in the reaction, highly optically enriched allylic alcohols were obtained. In this report (*R*)-MeO-BIPHEP furnished allylic alcohols with (*S*) stereochemistry.



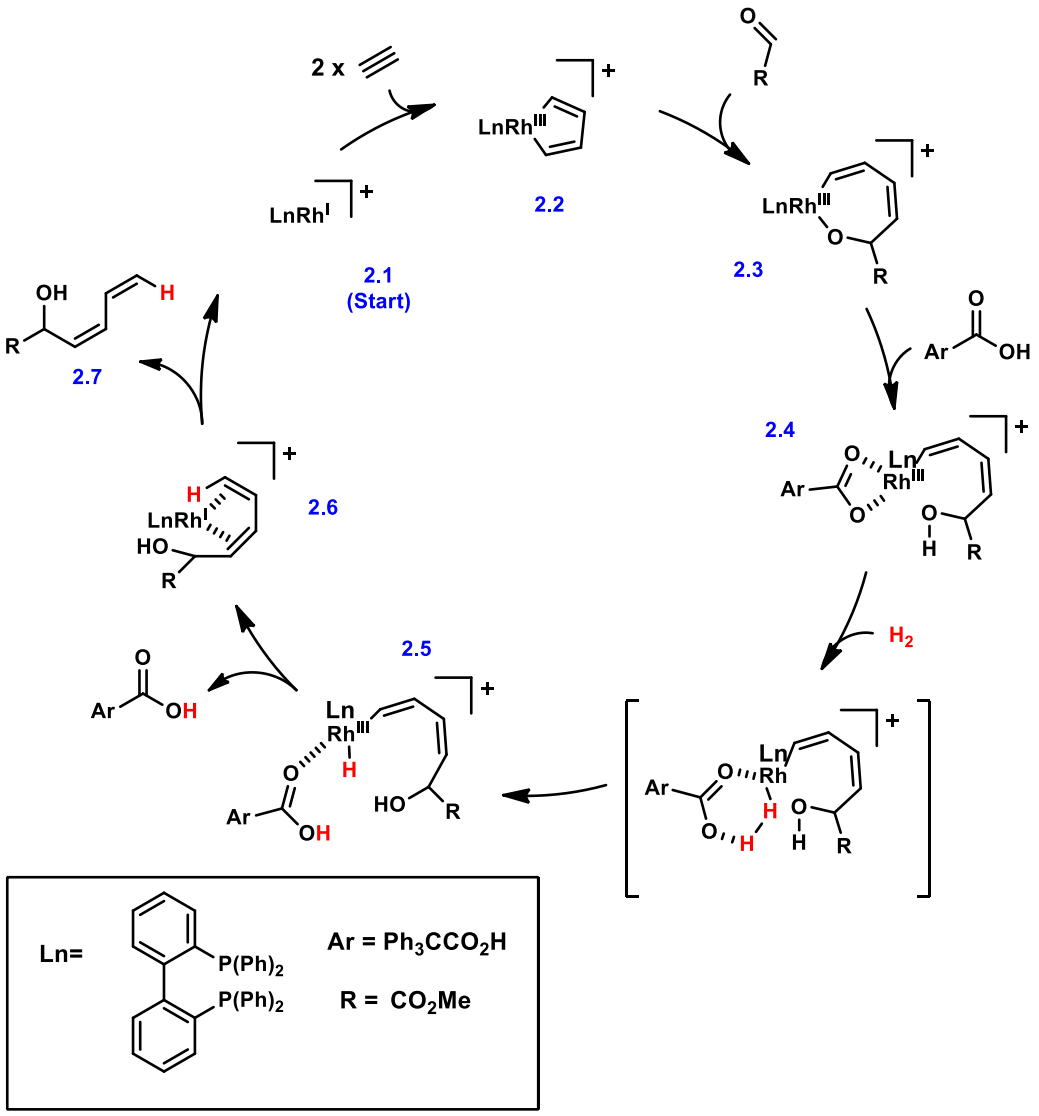
Scheme 2.5 Enantioselective (*Z*)-butadienylation via hydrogenative coupling

In a useful application of this unique reaction, Krische and co-workers reported catalyst directed hydrogenative couplings of acetylene to L-glyceraldehyde acetonide and other α-chiral aldehydes (Scheme 2.6).[53] Formal syntheses of eight L-hexoses were accomplished employing the hydrogenative (*Z*)-butadienylation from L-glyceraldehyde acetonide. This provided additional confirmation of stereochemistry and demonstrated the usefulness of this method. Interestingly, catalytic systems employing (*R*)-MeO-BIPHEP furnished allylic alcohols with (*R*) stereochemistry, this is the opposite direction of stereo-induction as the prior report (Scheme 2.5).



Scheme 2.6 Application of hydrogenative acetylene coupling

A mechanism for the hydrogenative (*Z*)-butadienylation was extensively studied through computational methods, detection of reaction intermediates with ESI mass spectrometric analyses, and diversion of intermediates into alternative reaction products.[54] The evidence gathered in those experiments supports the following mechanism (Scheme 2.7): starting at cationic rhodium **2.1**, two molecules of acetylene coordinate and dimerize to form a rhodacyclopentadiene **2.2**. This intermediate was detected with ESI mass spectrometric analysis and diverted into other products. From rhodacyclopentadiene **2.2**, carbonyl insertion of the aldehyde furnishes an intermediate oxa-rhodacycloheptadiene **2.3**. The rhodium oxygen bond cleavage is facilitated by the Brønsted acid co-catalyst; a hypothesis supported by computation, mass spectrometry, and diversion experiments. Protonation of the oxo moiety on the rhodacycle and binding of the carboxylate furnishes intermediate **2.4**. The carboxylate moiety can assist in H-H bond cleavage through a six-membered transition state to deliver complex **2.5**, which upon reductive elimination of a hydride furnishes **2.6**. Finally, disassociation of complex **2.6** provided the dienylation product **2.7** and cationic rhodium **2.1**, which can re-enter the catalytic cycle.



Scheme 2.7 Proposed mechanism hydrogenative acetylene coupling

2.3 Catalytic enantioselective carbonyl allylation and crotylation reactions

2.3.1 STOICHIOMETRIC ORGANOMETALLIC APPROACHES

The stereoselective construction of chiral homoallylic alcohols by addition of a chiral organometallic reagents to aldehydes has been among the most important methods for the construction of natural products.[55] Of the many reagents available for this transformation, chiral boron reagents have received the most attention since the first report by Hoffmann[56] (Figure 2.3). Significant contributions by Brown,[57,58] Roush, [59,60] Reetz, [61] and others[62] has led to a diverse class of similar reagents. However, these reagents require pre-activation and generate stoichiometric amounts of waste by-products, therefore they are considered inefficient in terms of atom economy.[37] The following section will focus on catalytic methods that have, in part, addressed these atom efficiency issues.

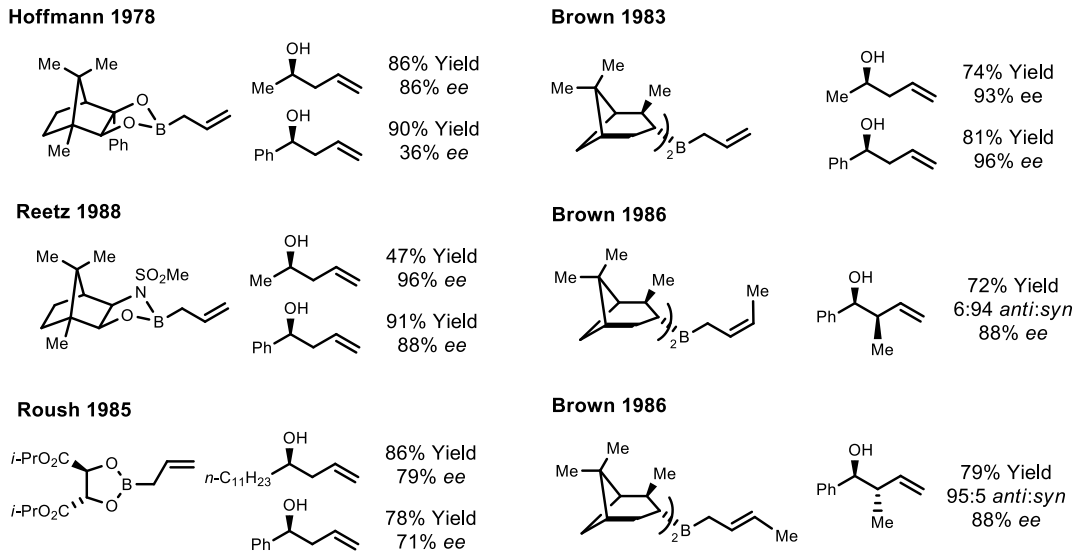
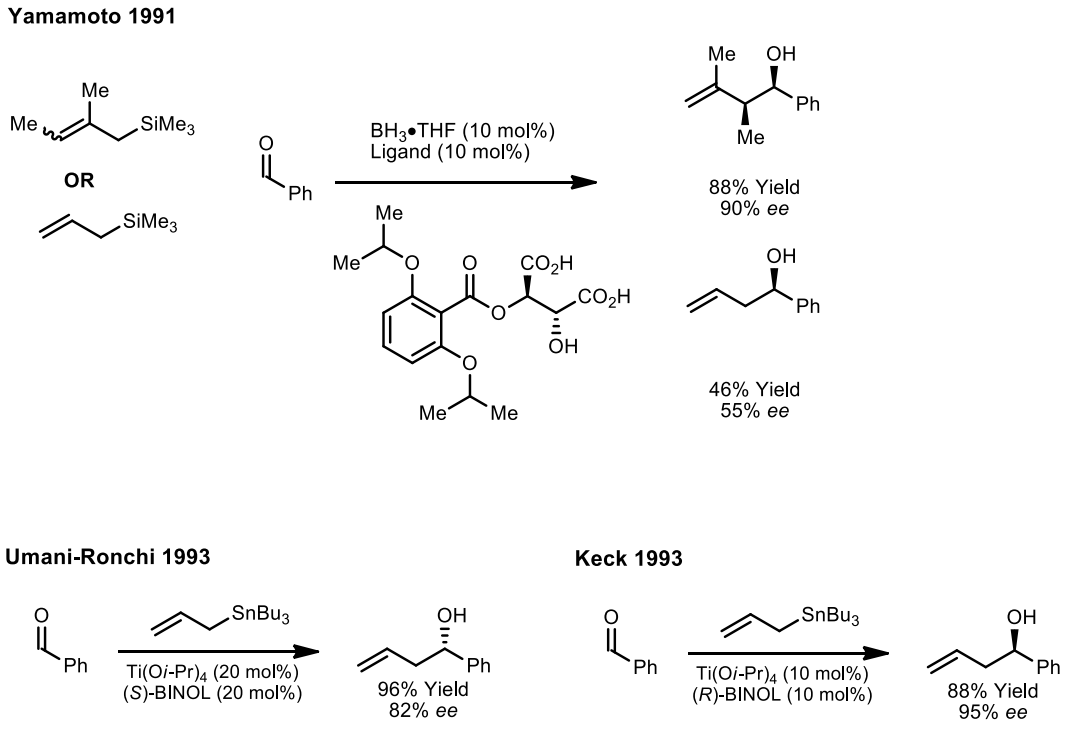


Figure 2.3 Reagents for enantioselective carbonyl allylation

2.3.1.1 Catalytic chiral Lewis acids and bases

The field of catalytic enantioselective allylations has seen significant growth over the past two decades since Yamamoto's report of the first examples of chiral Lewis acid-catalyzed enantioselective allylation of aldehydes (Scheme 2.8).[63] This protocol employed chiral acyloxy borane catalysts, which increased the electrophilicity of the aldehyde and furnished the products of methallylation and allylation. This breakthrough spurred further development of numerous chiral Lewis acids, which remains an active area of research.[62] In 1993, the laboratories of Umani-Ronchi [64] and Keck[65] independently reported highly enantioselective allylation protocols employing allyltin reagents with a BINOL modified titanium based Lewis acid catalyst. Although there have been numerous chiral Lewis acid systems developed, only the titanium based BINOL system has been reliably employed for complex systems.[66] Even though some chiral

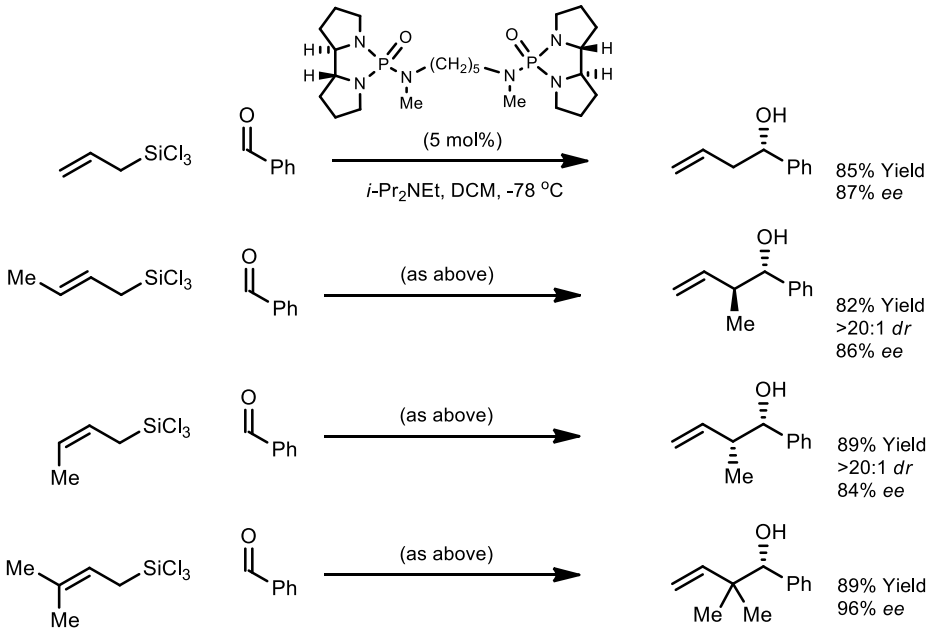
Lewis acid catalysis utilizes toxic tin based reagents, they can provide optically enriched homoallylic alcohols in high yields and selectivities. Further development of this area is needed to broaden the scope to include less toxic allyl donors and improve selectivity for substituted donors.



Scheme 2.8 Chiral Lewis acid catalyzed carbonyl allylations

An alternative approach to chiral Lewis acids, which activate the electrophile for nucleophilic addition, is chiral Lewis base catalysis. It involves the catalyst activating the allyl donor, thereby increasing its nucleophilicity, as well as coordinationing to the electrophile, which involves a six-centered transition structure.[67] This concept was initially brought to fruition by Denmark in 1994,[68] which upon further investigation of the mechanism[69] led to the development of a 2,2‘-bispyrrolidine-based bisphosphoramide

catalyst.[70] This new catalyst enabled a wide range of chlorosilane reagents to react with aldehydes furnishing products of allylation, crotylation, and prenylation in high yields and selectivities (Scheme 2.9).

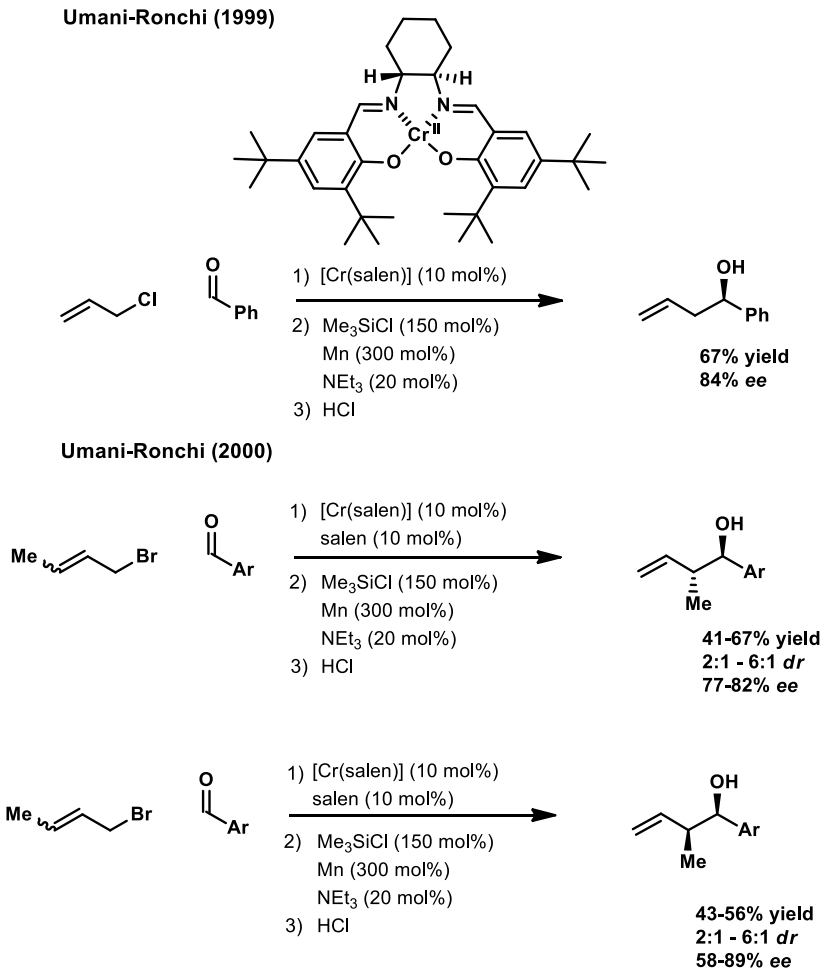


Scheme 2.9 Chiral Lewis base catalyzed carbonyl allylations

2.3.1.2 Catalytic enantioselective Nozaki–Hiyama–Kishi reactions

After the original reports of the Nozaki–Hiyama–Kishi (NHK) reaction, there have been numerous efforts to develop a catalytic enantioselective version of this reaction.[71] A protocol developed by Fürstner and co-workers required catalytic amounts of chromium, employed manganese as a reducing agent, and a trialkylchlorosilane to perpetuate the reaction.[72] That important breakthrough was followed by a report from the laboratory of Umani-Ronchi, which employed a chirally modified chromium salen complex and Fürstner's modified conditions to affect the first catalytic enantioselective

allylation (Scheme 2.10).[73] Further development of this protocol led to a selective crotylation,[74] and a method to obtain the opposite diastereoselectivity (Scheme 2.10).[75] Although the yields and selectivity were moderate, it did demonstrate the feasibility of asymmetric induction via salen modified catalysts. Chiral ligand development for the NHK reaction has continued to receive attention from the scientific community, and several improvements have been made to expand the scope of allylic halides that react with aromatic and aliphatic aldehydes at synthetically useful levels of selectivity.[71,76]

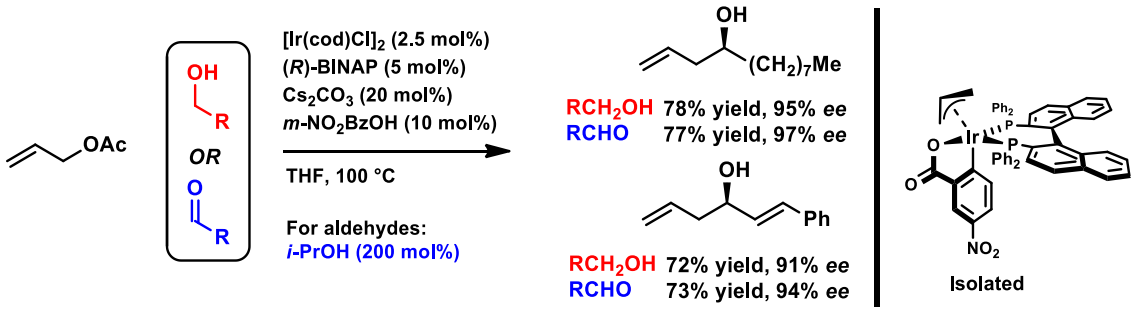


Scheme 2.10 Catalytic enantioselective Nozaki–Hiyama–Kishi reactions

2.3.2 ENANTIOSELECTIVE IRIDIUM-CATALYZED TRANSFER HYDROGENATIVE CARBONYL ALLYLATION AND CROTYLATION

The traditional reactivity for allyliridium intermediates can be characterized as electrophiles, which will undergo addition from nucleophiles.[77] In 2008, Krische and co-workers reported an inversion of this reactivity, where instead of the allyl donor reacting with electrophilic character, the allyliridium complex demonstrated nucleophilic

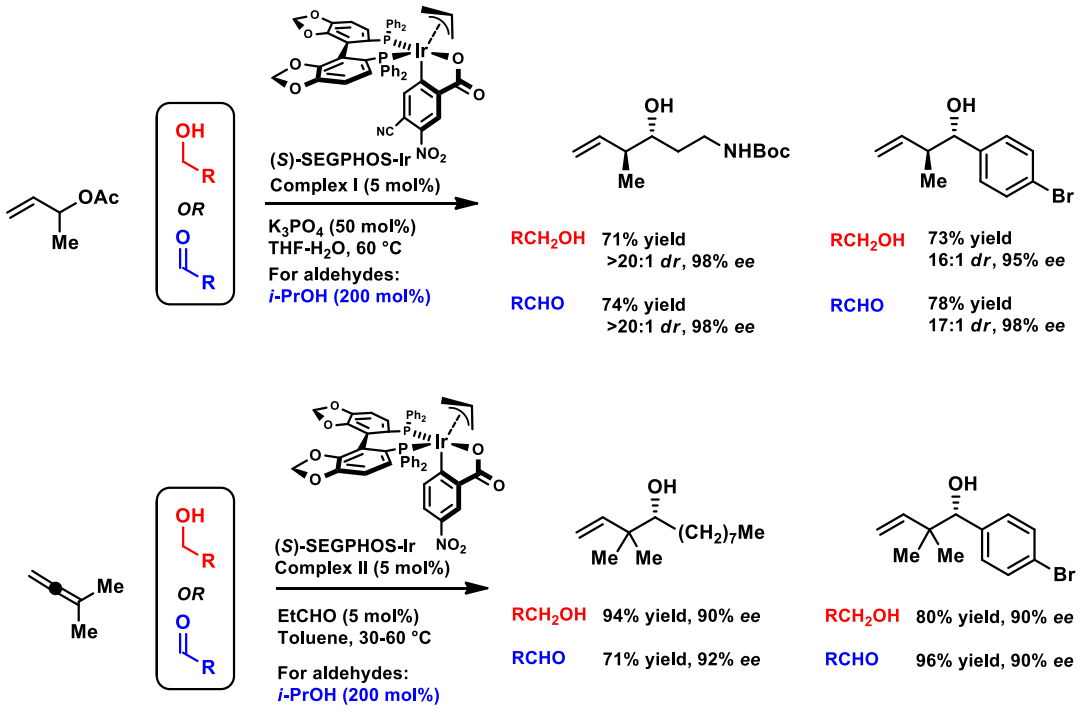
character by providing the products of carbonyl addition. [78] The use of both an acid and base additive in the reaction, seems counter-intuitive, but further investigation revealed that both additives were required to facilitate formation of the cyclometallated iridium-catalyst (Scheme 2.11).[79] A single-crystal X-ray diffraction analysis confirmed the structure of cyclometallated catalyst and the complex was found to be a relevant intermediate in the proposed catalytic cycle. The reaction scope was broad with respect to aldehydes and alcohols furnishing the products of carbonyl allylation in uniformly high yields and selectivity. Most importantly, this new method obviated the use of stoichiometric amounts of pre-metallated reagents. These aspects of the reaction warranted further investigation into the scope of allyl donors and electrophilic substrates.



Scheme 2.11 Enantioselective iridium-catalyzed transfer hydrogenative allylation

Following the initial report that α-methyl allyl acetate would affect carbonyl crotylation,[78] it was found that when the cyclo-metallated iridium complex was employed as a precatalyst, products of carbonyl crotylation were obtained in good to excellent yield with *anti*-diastereoselectivity (Scheme 2.12). [80,81] A variation of the precatalyst has shown to be highly effective in the reductive coupling of 1,1-dimethylallene to aromatic and

aliphatic alcohols or aldehydes providing products of reverse prenylation in good yields and selectivity.[82] These reactions employ variations of the cyclometallated iridium π-allyl *C*,*O*-benzoate complexes and are stable enough that they can be purified via column chromatography.[83] The continued investigation of new allyl donors and precatalysts by Krische and co-workers has led to a new family of carbonyl allylation processes (Figure 2.4).[84,85]



Scheme 2.12 Enantioselective iridium-catalyzed transfer hydrogenative crotylation and reverse prenylation

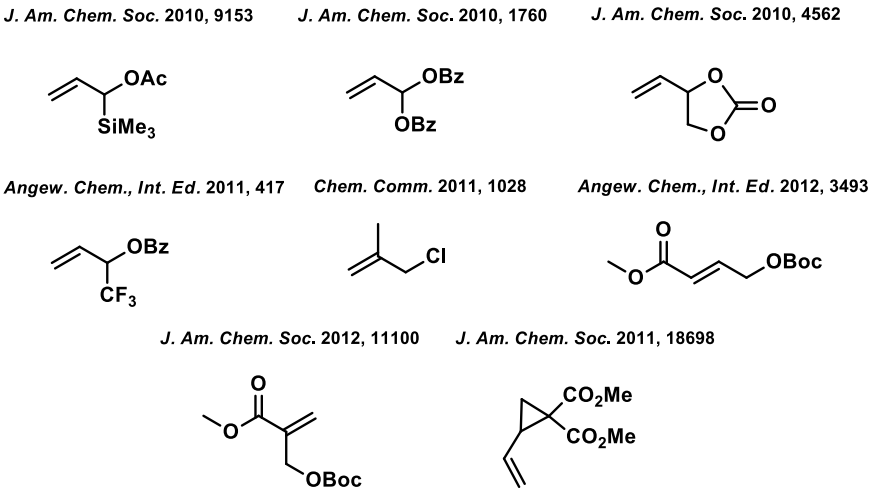


Figure 2.4 Scope of allyl donors

A general mechanism based on the collective data has been proposed, which begins with an iridium catalyst dehydrogenating the reactant alcohol through a *β*-hydride elimination to produce an aldehyde and an iridium hydride (Figure 2.5).[86] The hydride complex can be deprotonated to generate an anionic iridium intermediate, which then reacts with the allyl donor to furnish the allyliridium intermediate. This allylmetal intermediate can react with the aldehyde component through a closed six-center transition state, which serves as the basis for the high levels of *anti*-diastereoselectivity observed. Finally, protonolysis of the newly formed iridium alkoxide with the reactant alcohol furnishes the crotylation product and regeneration of reactive intermediates so that the catalytic cycle can continue.

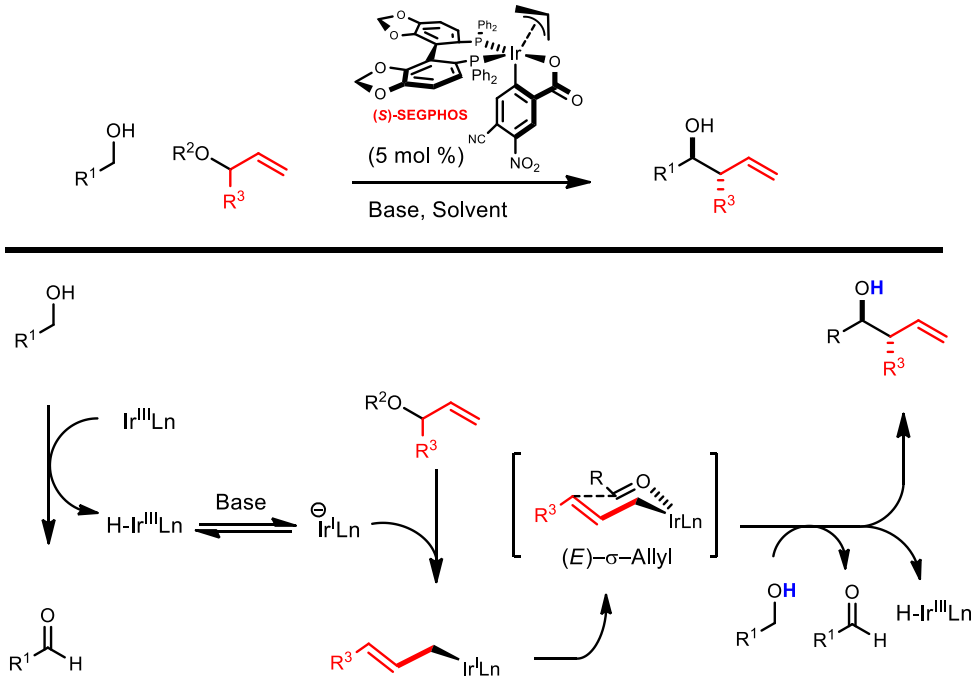
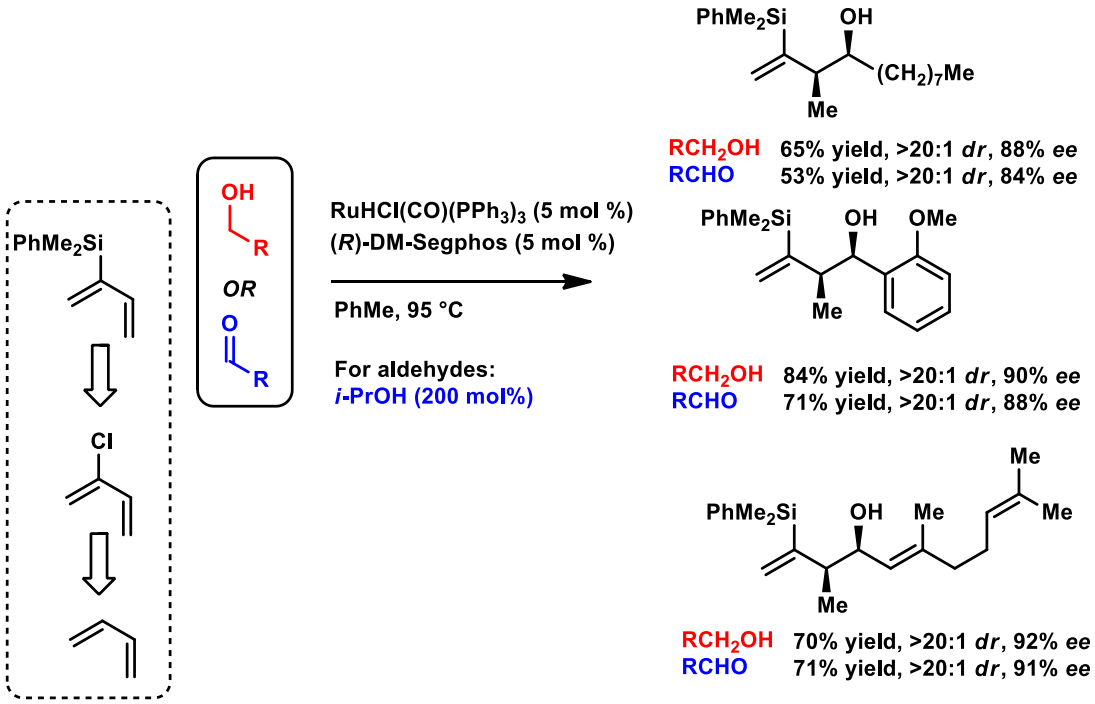


Figure 2.5 Proposed general mechanism for iridium-catalyzed transfer hydrogenative couplings

2.3.3 ENANTIOSELECTIVE RUTHENIUM-CATALYZED CARBONYL CROTYLATION

Significant progress was made with iridium-catalyzed transfer hydrogenative couplings, but those protocols were unable to provide highly selective *syn*-diastereoselective crotylation or utilize butadiene for highly selective transformations.[87] Efforts to develop a highly *syn*-diastereoselective crotylation process led to the investigation of silyl-substituted dienes and ruthenium based catalysts that would adopt a transition state geometry required to access the *syn* isomer. Exposure of alcohols or aldehydes to a 2-silyl-substituted diene, in the presence of ruthenium catalyst modified by a chiral ligand furnished products of *syn*-diastereo- and enantioselective carbonyl crotylation (Scheme 2.13).[88,89] A brief exploration of the substrate scope revealed that a range of aliphatic, allylic, aromatic substrates were able to furnish the respective crotylation products in good yield with excellent levels of the selectivity. This was an important milestone in the development of catalytic systems that would use butadiene as an allyl donor to circumvent pre-activation and deliver products of carbonyl crotylation without any stoichiometric metal waste.



Scheme 2.13 Enantioselective ruthenium-catalyzed *syn*-crotylation

A plausible catalytic mechanism begins with the ruthenium catalyst dehydrogenating the reactant alcohol through a *β*-hydride elimination to produce an aldehyde and a ruthenium hydride (Figure 2.6). This metal-hydride can react with the diene by adding the hydride and metal across the diene to generate an allylruthenium intermediate. This allylmetal intermediate can react with the aldehyde component through a closed six-center transition state. The silyl group forces the allyl geometry into a pseudo (*Z*)-σ-allyl haptomer, thus conferring high levels of the *syn*-diastereoselectivity. Finally, protonolysis of the newly formed ruthenium alkoxide by the reactant alcohol furnishes the crotylation product with regeneration of the reactive intermediates so that the catalytic cycle can continue.

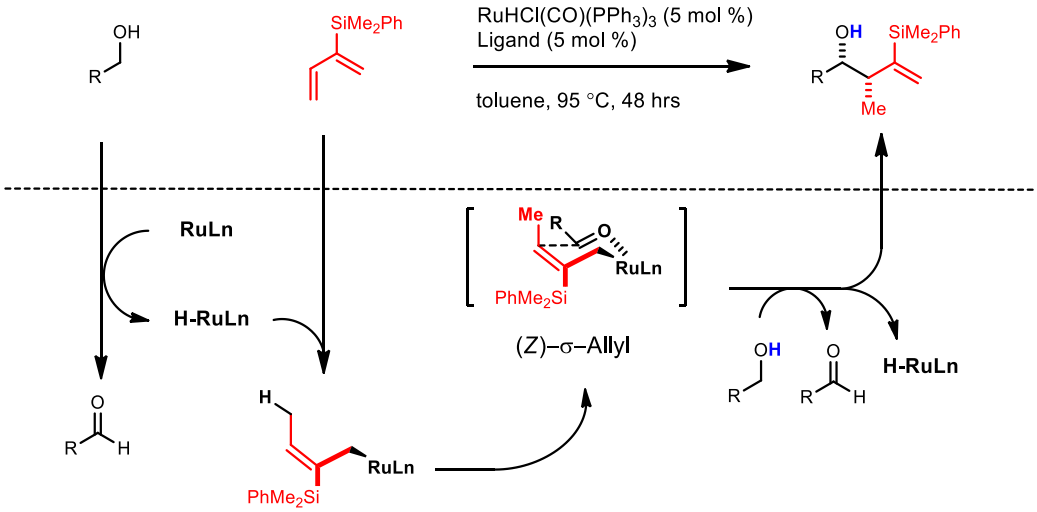
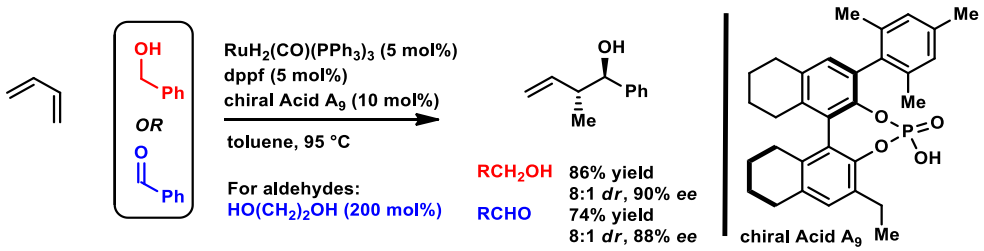


Figure 2.6 Proposed general mechanism for the ruthenium-catalyzed carbonyl crotylation[89]

In 2012, Krische and co-workers reported a major breakthrough toward their ultimate goal of developing by-product-free carbonyl addition processes. [90] Exposure of alcohols or aldehydes to butadiene, in the presence of ruthenium catalyst modified by a chiral phosphoric acid led to products of *anti*-diastereo- and enantioselective carbonyl crotylation (Scheme 2.14). Further study of the ruthenium catalysts modified by both chiral counter ions and ligands led to the development of protocols to control all aspects of diastereo- and enantioselective carbonyl crotylation with butadiene.[91]



Scheme 2.14 Enantioselective ruthenium-catalyzed *anti*-crotylation [90]

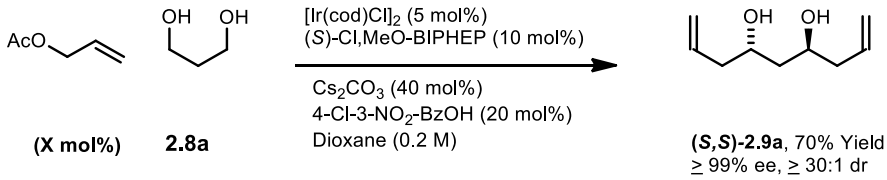
2.4 Two directional allylation

Nature's vast collection of polyketide natural products includes many compounds incorporating polyacetate derived 1,3-diol or higher 1,3-polyol substructures. While there are numerous protocols for the synthesis of these structural motifs, the iterative allylmetallation of aldehydes has found exceptionally broad use.[92,93] For example, asymmetric iterative allylchromation (Nozaki-Hiyama-Kishi coupling),[94] allyltitanation,[95,96] allylstannation,[97,98] allylsilation,[99,100] and allylboration[101,102,103] have been employed in synthetic approaches to 1,3-diols and higher homologues. Despite these advances, use of traditional allylmetallation protocols in iterative two-directional syntheses of 1,3-polyol substructures is prohibited by the instability of malondialdehyde.

In connection with ongoing efforts to exploit catalytic hydrogenation in C-C couplings beyond hydroformylation,[86,85,88] an enantioselective protocol for carbonyl allylation from the alcohol oxidation level was developed in the Krische laboratory under the conditions of iridium-catalyzed transfer hydrogenation employing allyl acetate as an allyl donor.[78,79] Here, the reactant alcohol serves dually as a source of hydrogen and as an aldehyde precursor, enabling the formation of highly optically enriched homoallylic alcohols directly from the alcohol oxidation level by way of a transient aldehyde. Using a chiral iridium *C*,*O*-benzoate complex modified by 4-chloro-3-nitrobenzoic acid and (*R*)- or (*S*)-Cl, MeO-BIPHEP, we reported an iterative two-directional *bis*-allylation of glycols, as demonstrated by the rapid assembly of protected 1,3-polyol substructures with exceptional levels of enantiocontrol and catalyst-directed diastereoselectivity.[104] Notably,

this process successfully exploits 1,3-diols as synthetic equivalents to unstable malondialdehydes.

Malondialdehyde is highly unstable and cannot be isolated in pure form. Although malondialdehyde can be generated through the hydrolysis of 1,1,3,3-tetramethoxypropane, capture of this highly unstable dialdehyde is impeded by the fact that it is generated in an aqueous environment, which promotes hydration, oligomerization, self-condensation and precludes the use of many organometallic reagents. The ability to bypass stoichiometric pre-formation of aldehyde electrophiles in carbonyl allylation offers the opportunity to conduct allylations that cannot be performed efficiently from the aldehyde oxidation level. We reasoned that 1,3-propanediols could serve as a synthetic equivalent to malondialdehyde via successive generation and capture of mono-aldehyde intermediates. Accordingly, the asymmetric allylation of propylene glycol **2.8a** was explored. To our delight, using the cyclometallated catalyst generated *in situ* from $[Ir(cod)Cl]_2$ (5 mol%), (*S*)-Cl,MeO-BIPHEP (10 mol%), 4-chloro-3-nitrobenzoic acid (20 mol%) and Cs_2CO_3 (40 mol%) in dioxane solvent (0.2 M), the coupling of allyl acetate (1000 mol%) to **2.8a** at 90 ^{o}C delivers the C_2-symmetric homoallylic diol (*S*,*S*)-**2.9a** in 70% isolated yield and ≥ 99% enantiomeric excess with ≥30:1 diastereoselectivity, as determined by chiral stationary phase HPLC analysis (Table 2.1). A decrease in the loading of allyl acetate from 10 to 5 equivalents diminished the isolated yield of (*S*,*S*)-**2.9a** to 43% (entry 6).

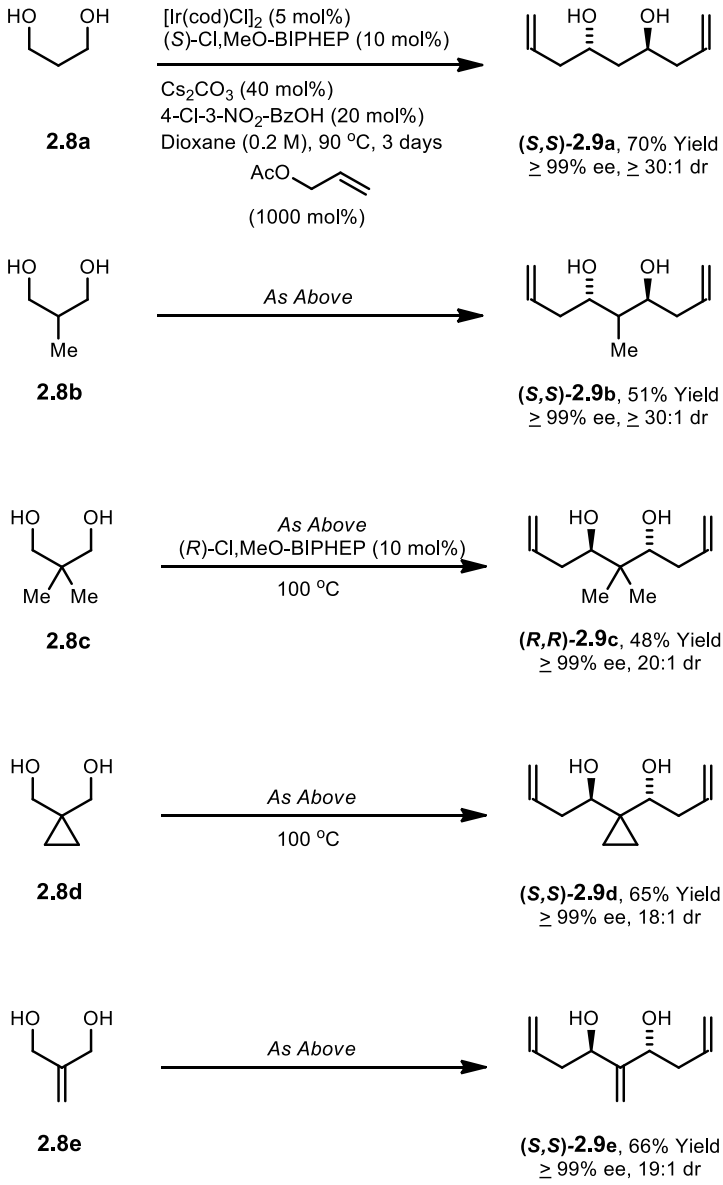


Entry[a]	X mol%	T (°C)	Time (h)	2.9a (% yield)
1	1000	90	24	56
2	1000	90	48	63
3	**1000**	**90**	**72**	**70**
4	1000	90	96	66
5	500	80	72	50
6	500	90	72	43

[a] Reactions run with the help of Drs. In Su Kim, Yu Lu, and Abbas Hassan

Table 2.1 Optimization of two-directional allylation

These conditions were applied to propylene glycols **2.8b-2.8e** (Scheme 2.15). Although yields were slightly diminished in the case of 2-methyl-1,3-propanediol **2.8b** and 2,2-dimethyl-1,3-propanediol (neopentyl glycol) **2.8c**, uniformly high levels of enantioselectivity were observed in all cases (≥ 99% *ee*). Efficient *bis*-allylation of 2-methylene-1,3-propanediol **2.8e** is especially remarkable in view of the exceptional instability anticipated for the corresponding dialdehyde, which to our knowledge, has not been reported in the literature.



Scheme 2.15 Diol substrates for two-directional allylation

Since the initial report of this strategy for two directional allylation, this method has been used in the construction of a variety of polyketide natural products. For example, as highlighted in blue in Figure 2.7, syntheses of roxaticin,[105] bryostatin 7,[106,107] cyanolide A,[108] and a fragment toward the synthesis of tetrafibricin[109] have successfully

utilized diols as substrates for an iterative two-directional allylation in the assembly of these polyketide natural products.

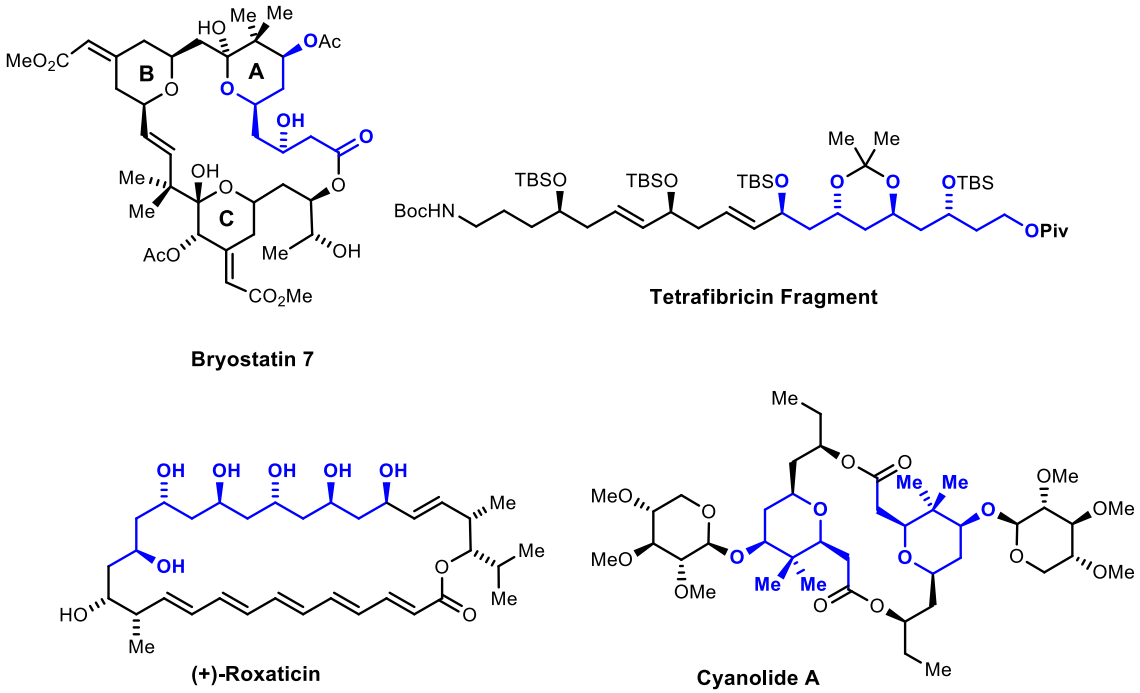


Figure 2.7 Applications of two-directional allylation in total synthesis

2.5 Conclusions

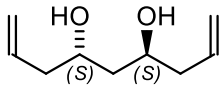
In review, classical methods for the construction of chiral allylic and homo-allylic alcohols through carbonyl vinylation, allylation, and crotylation are effective. However, they are often accompanied with significant pre-activation and stoichiometric waste generation. As an alternative method for the assembly of those structural motifs, C-C bond forming hydrogenation has emerged as a general process to rapidly build more complex moieties from simple achiral building blocks while reducing pre-activation and stoichiometric waste generation. An example of this transformation was demonstrated in

the two directional allylation of diols under the conditions of iridium-catalyzed C-C bond forming transfer hydrogenation. Diverse glycols **2.8a-2.8e** were subjected to highly enantioselective carbonyl allylation from the alcohol oxidation level to furnish the corresponding C2-symmetric diols **2.9a-2.9e**. The development of new catalysts for C-C bond forming hydrogenation is progressing synthetic organic chemistry toward new levels of efficiency with by-product free methods that can utilize simple feedstock chemicals for asymmetric transformations.

2.6 Experimental

General Methods

All reactions were run under an atmosphere of nitrogen. Tetrahydrofuran (THF) was obtained from Pure-Solv MD-5 Solvent Purification System (Innovative Technology). Anhydrous 1,4-dioxane was distilled over Na/benzophenone prior to use. Sealed tubes (13x100 mL) were purchased from Fischer Scientific and were dried in oven overnight and cooled under a stream of nitrogen prior to use. Commercially available allyl acetate (Aldrich) and diols were purified by distillation or recrystallization prior to use. Cesium carbonate were purchased from Alfa Aesar and used directly without further purification. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}). Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H or M+Na). Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded with a Varian Gemini (400 MHz) spectrometer for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm), respectively, as internal standards. Coupling constants are reported in Hertz (Hz).



(*S*,*S*)-2.9a

(4*S*,6*S*)-Nona-l,8-diene-4,6-diol ((*S*,*S*)-2.9a)

To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (13.4 mg, 0.02 mmol, 5 mol%), (*S*)-Cl,MeO-BIPHEP (26.1 mg, 0.04 mmol, 10 mol%), Cs_2CO_3 (52.1 mg, 0.16 mmol, 40 mol%) and 4-chloro-3-nitrobenzoic acid (16.1 mg, 0.08 mmol, 20 mol%) was added 1,4-dioxane (1.0 mL) followed by allyl acetate (0.4 g, 4 mmol, 1000 mol%). The reaction mixture was allowed to stir at 90 ^{o}C for 0.5 hr and was then allowed to cool to room temperature. 1,3-Propanediol **2.8a** (30.4 mg, 0.4 mmol, 100 mol%) in 1,4-dioxane (1.0 mL) was added to the reaction mixture and the reaction mixture was allowed to stir at 90 ^{o}C for 3 days, at which point the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes, 1:4 to 1:2 with 0.1% TEA) provided **(*S*,*S*)-2.9a** (43.6 mg, 0.279 mmol, dr ≥ 30:1) as a colorless oil in 70% yield.

TLC (SiO_2): R_f = 0.44 (ethyl acetate:hexanes, 1:1).

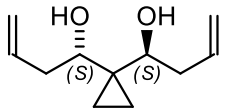
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86-5.77 (m, 2H), 5.16-5.10 (m, 4H), 4.02-3.96 (m, 2H), 2.59 (s, 2H), 2.28-2.24 (m, 4H), 1.64-1.62 (t, *J* = 6.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.6, 118.1, 68.1, 42.0, 41.5.

FTIR (neat): υ 3354, 3078, 2980, 2932, 2909, 2838, 1717, 1632, 1432, 1330, 1245, 1067, 1045, 996, 907 cm^{-1}.

HRMS (CI) Calcd. for $C_9H_{17}O_2$ $(M+H)^+$: 157.1229, Found: 157.1225.

HPLC: Enantiomeric excess was determined by HPLC analysis of bis-4-nitro-benzoate derivative of the product. (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm), t_{major} = 17.0 min, t_{minor} = 37.9 min; ee > 99%.



(*S*,*S*)-2.9d

(1*S*,1'*S*)-1,1'-(Cyclopropane-1,1-diyl)dibut-3-en-1-ol ((*S*,*S*)-2.9d)

To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (13.4 mg, 0.02 mmol, 5 mol%), (*S*)-Cl,MeO-BIPHEP (26.1 mg, 0.04 mmol, 10 mol%), Cs_2CO_3 (52.1 mg, 0.16 mmol, 40 mol%) and 4-chloro-3-nitrobenzoic acid (16.1 mg, 0.08 mmol, 20 mol%) was added 1,4-dioxane (1.0 mL) followed by allyl acetate (0.4 g, 4 mmol, 1000 mol%). The reaction mixture was allowed to stir at 90 ^{o}C for 0.5 hr and was then allowed to cool to room temperature. 1,1-Bis(hydroxymethyl)cyclopropane **2.8d** (40.9 mg, 0.4 mmol, 100 mol%) in 1,4-dioxane (1.0 mL) was added to the reaction mixture and the reaction mixture was allowed to stir at 100 ^{o}C for 3 days, at which point the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes, 1:6 to 1:3 with 0.1% TEA) provided **(*S*,*S*)-2.9d** (47.5 mg, 0.261 mmol, dr =18:1) as a colorless oil in 65% yield.

TLC (SiO_2): R_f = 0.30 (ethyl acetate:hexanes, 1:4).

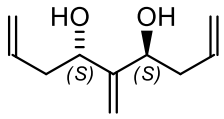
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86-5.76 (m, 2H), 5.13-5.06 (m, 4H), 3.58-3.53 (m, 2H), 3.31 (s, 2H), 2.19-2.14 (m, 4H), 0.55-0.51 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.5, 117.8, 75.4, 38.3, 27.8, 8.3.

FTIR (neat): υ 3377, 3074, 3007, 2976, 2905, 2357, 2326, 1699, 1637, 1423, 1294, 1249, 1049, 1027, 982, 907 cm^{-1}.

HRMS (CI) Calcd. for $C_{11}H_{19}O_2$ $(M+H)^+$: 183.1385, Found: 183.1384.

HPLC: Enantiomeric excess was determined by HPLC analysis of bis-4-nitro-benzoate derivative of the product. (Chiralpak AD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm), t_{major} = 20.7 min, t_{minor} = 22.9 min; ee > 99%.



(*S*,*S*)-2.9e

(4*S*,6*S*)-5-Methylenenona-1,8-diene-4,6-diol ((*S*,*S*)-2.9e)

To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (13.4 mg, 0.02 mmol, 5 mol%), (*S*)-Cl,MeO-BIPHEP (26.1 mg, 0.04 mmol, 10 mol%), Cs_2CO_3 (52.1 mg, 0.16 mmol, 40 mol%) and 4-chloro-3-nitrobenzoic acid (16.1 mg, 0.08 mmol, 20 mol%) was added 1,4-dioxane (1.0 mL) followed by allyl acetate (0.4 g, 4 mmol, 1000 mol%). The reaction mixture was allowed to stir at 90 ^oC for 0.5 hr and was then allowed to cool to room temperature. 2-Methylene-1,3-propanediol **2.8e** (35.2 mg, 0.4 mmol, 100 mol%) in 1,4-dioxane (1.0 mL) was added to the reaction

mixture and the reaction mixture was allowed to stir at 90 ^{o}C for 3 days, at which point the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes, 1:5 to 1:3 with 0.1% TEA) provided **(*S*,*S*)-2.9e** (44.4 mg, 0.264 mmol, dr =19:1) as a colorless oil in 66% yield.

TLC (SiO_2): R_f = 0.35 (ethyl acetate:hexanes, 1:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86-5.75 (m, 2H), 5.17-5.12 (m, 4H), 4.25 (t, *J* = 6.4 Hz, 2H), 2.70 (s, 2H), 2.46-2.36 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1, 134.7, 118.5, 112.5, 72.3, 40.8.

FTIR (neat): υ 3372, 3069, 2980, 2909, 2932, 1637, 1419, 1307, 1254, 1045, 987, 911 cm^{-1}.

HRMS (CI) Calcd. for $C_{11}H_{19}O_2$ $(M+H)^+$: 183.1385, Found: 183.1384.

HPLC: Enantiomeric excess was determined by HPLC analysis of bis-4-nitro-benzoate derivative of the product. (Chiralpak AD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm), t_{minor} = 20.3 min, t_{major} = 22.6 min; ee > 99%.

2.7 Spectra relevant to chapter 2

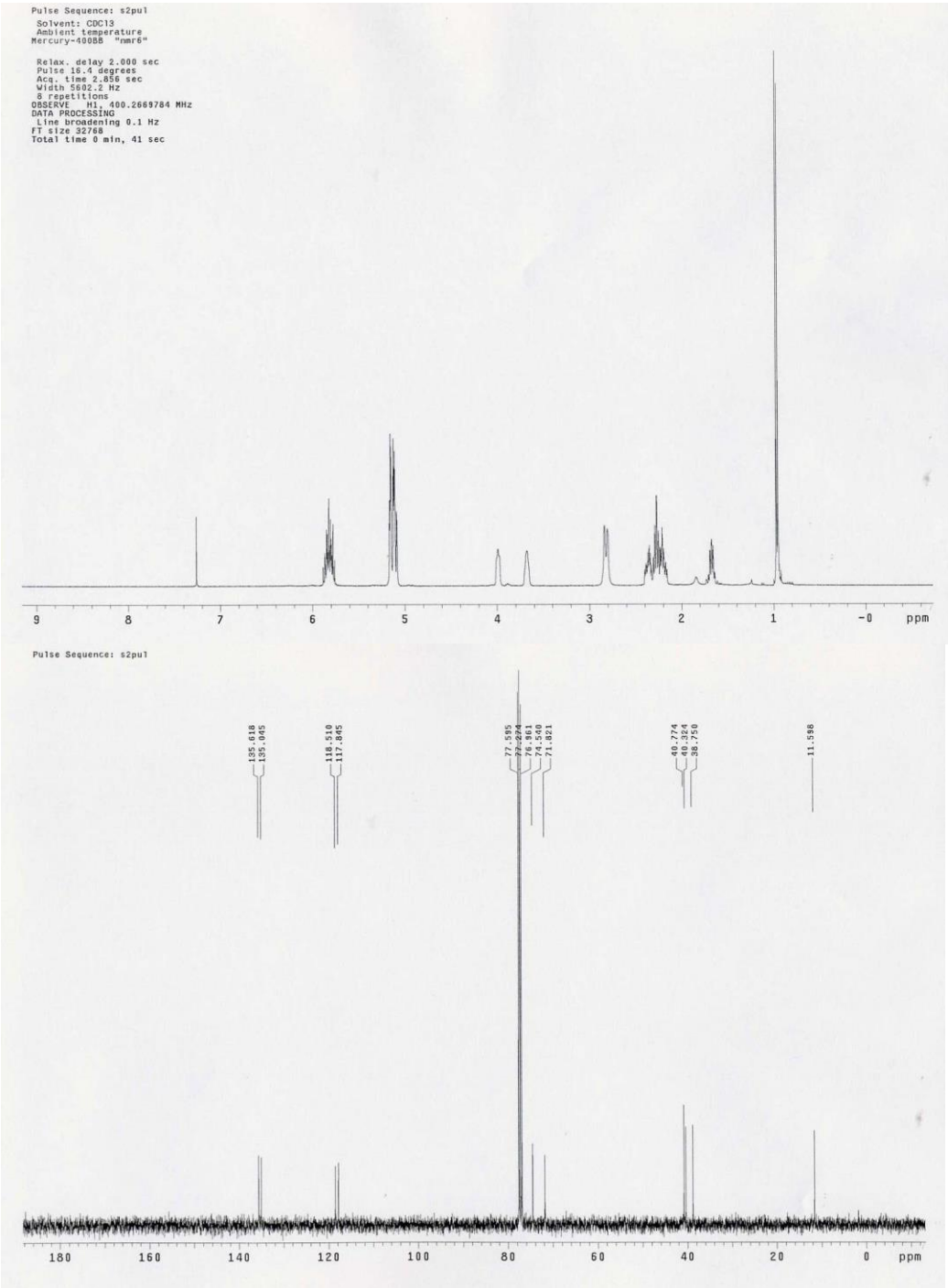
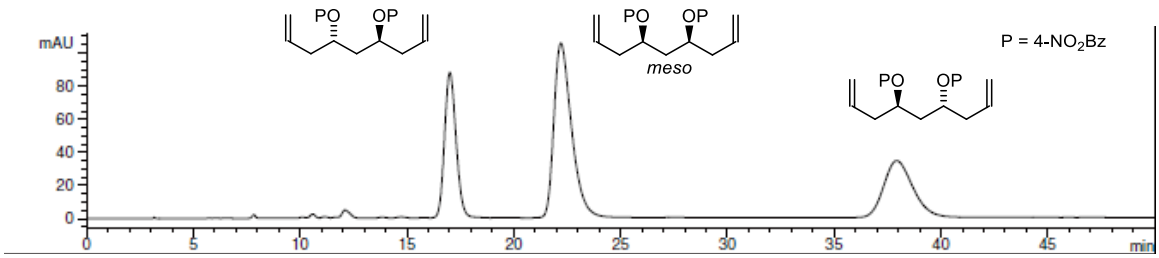
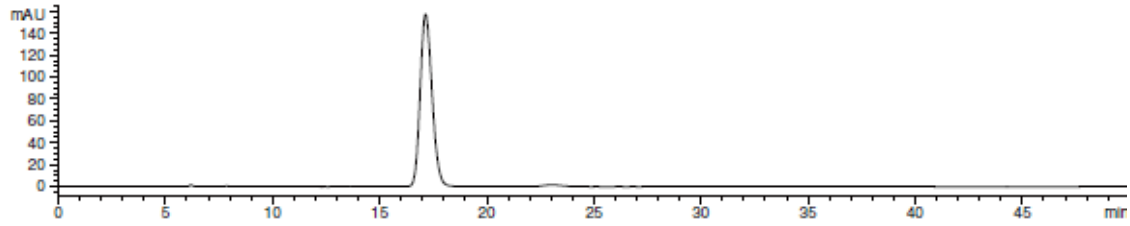


Figure 2.8 ^{1}H and ^{13}C NMR spectra of compound **2.9a**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.006	VB	0.5875	3306.10620	87.76276	26.1454
2	22.204	BB	0.8760	6071.38721	105.39973	48.0139
3	37.922	BB	1.4680	3267.57324	34.40439	25.8407
Totals :				1.26451e4	227.56689	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.146	BB	0.5999	6066.44531	157.31107	98.4234
2	23.037	BB	0.8187	97.17281	1.53046	1.5766
Totals :				6163.61812	158.84153	

Figure 2.9 HPLC data for compound **2.9a**

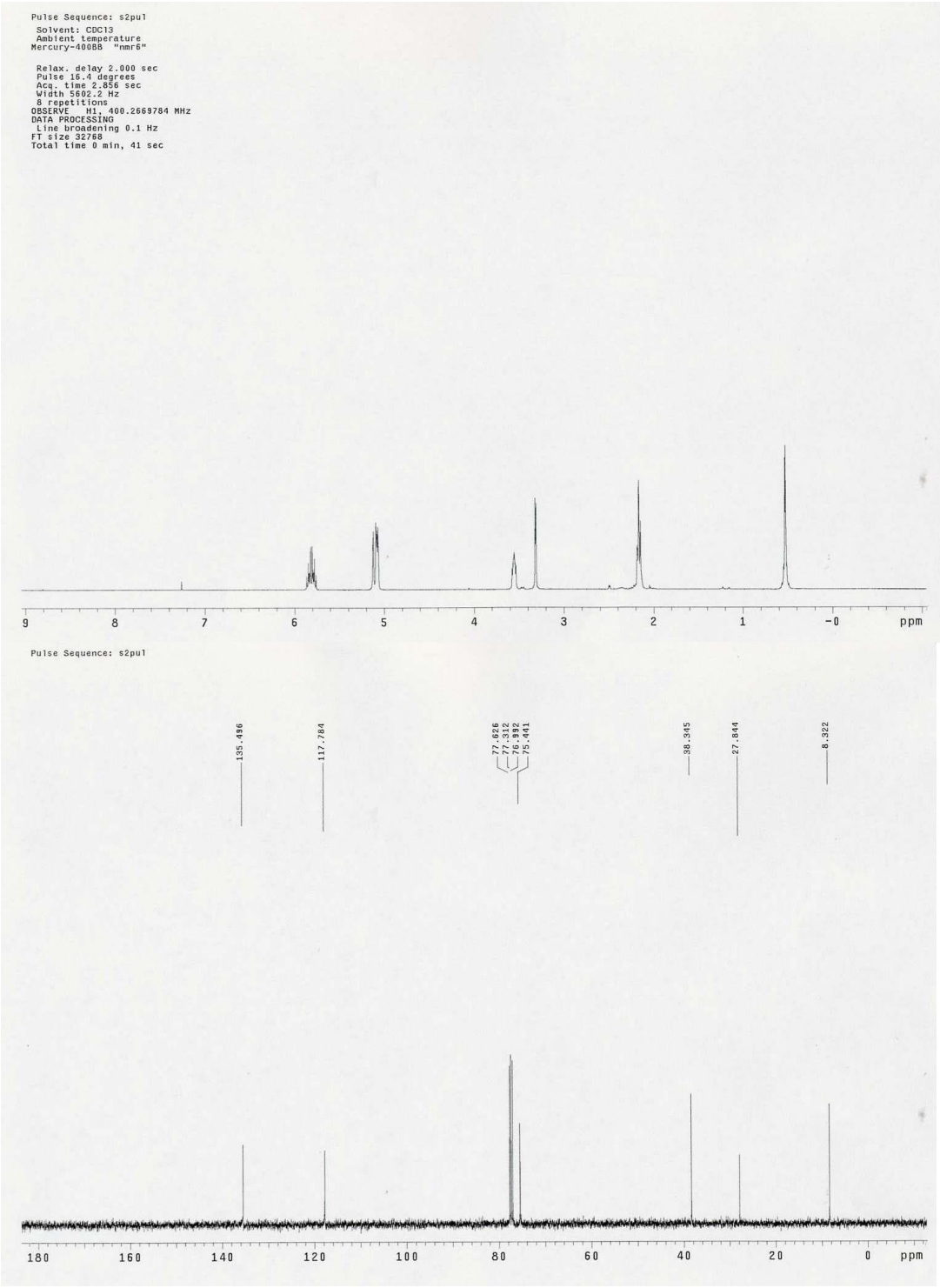
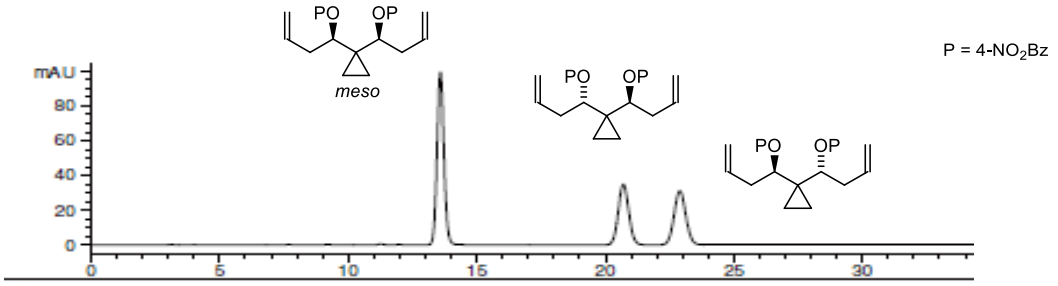
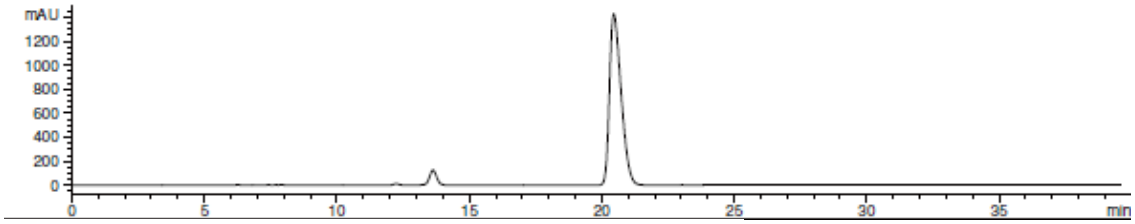


Figure 2.10 ^{1}H and ^{13}C NMR spectra of compound **2.9d**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.589	BB	0.2915	1867.21924	99.24776	48.6018
2	20.707	BB	0.4441	990.42560	34.79167	25.7797
3	22.903	BB	0.4948	984.23083	30.96489	25.6185
Totals :				3841.87567	165.00432	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.631	BB	0.2965	2385.70435	123.95669	5.1848
2	20.456	BB	0.4690	4.36274e4	1425.63464	94.8152
Totals :				4.60131e4	1549.59133	

Figure 2.11 HPLC data for compound **2.9d**

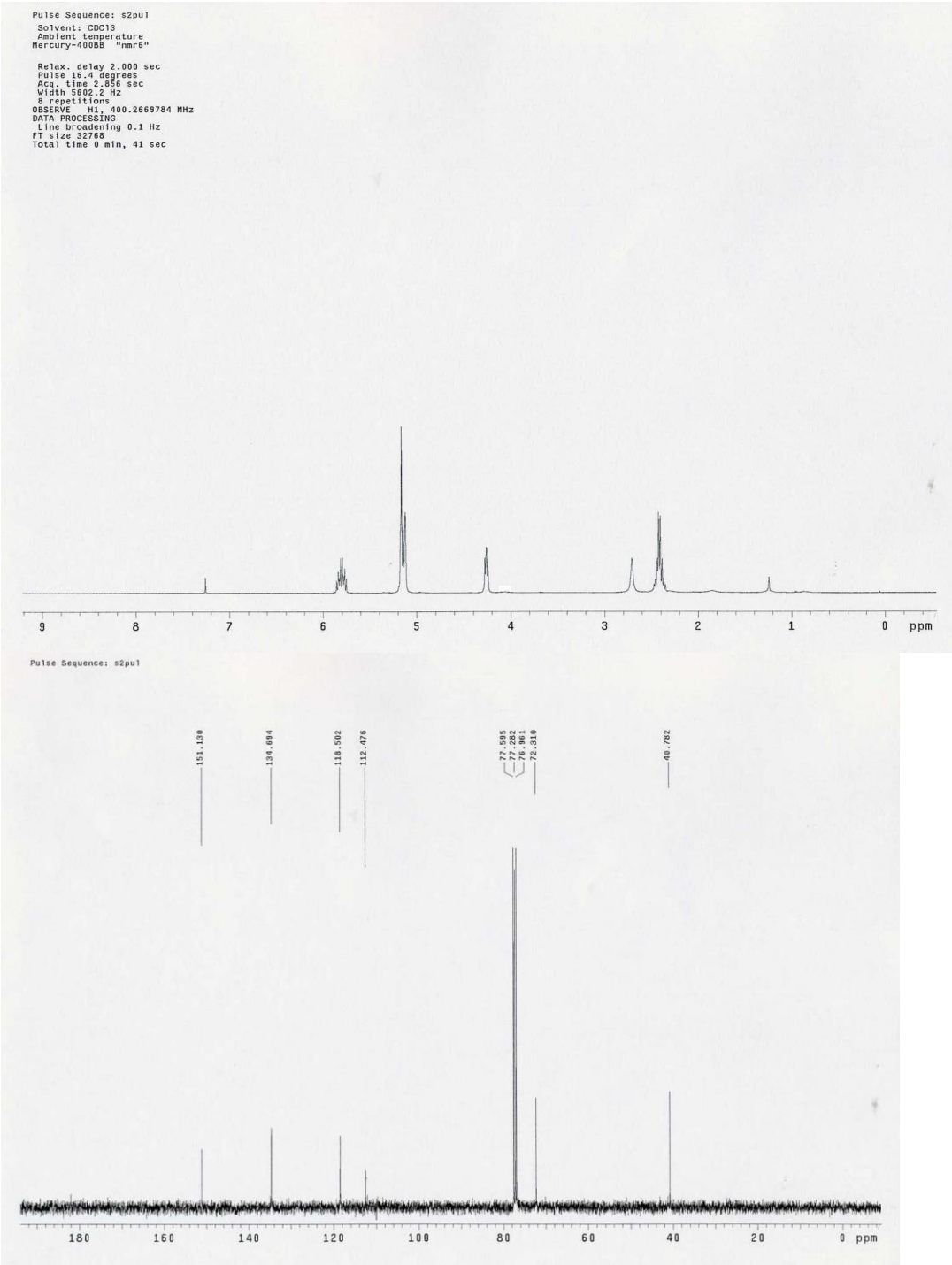
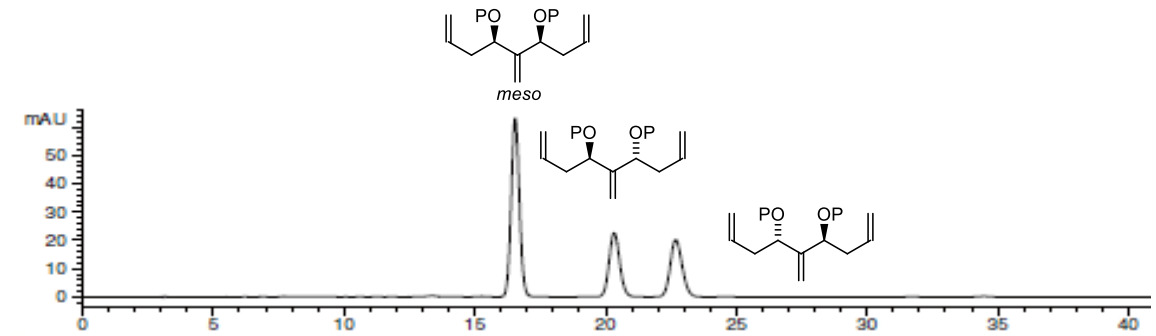
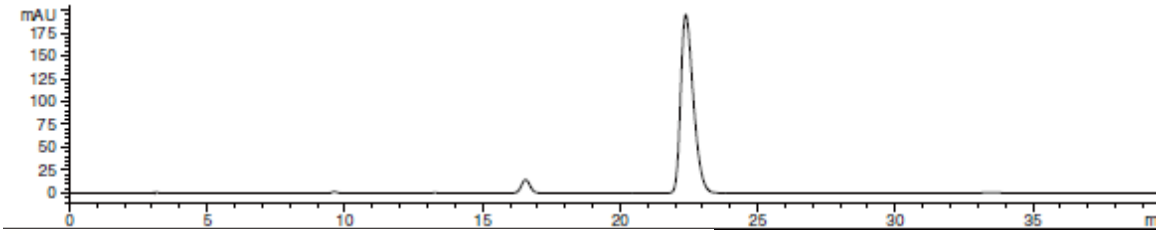


Figure 2.12 ^{1}H and ^{13}C NMR spectra of compound **2.9e**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.546	VB	0.3434	1389.79346	62.99154	51.9005
2	20.330	VB	0.4391	641.53650	22.60326	23.9576
3	22.684	BB	0.4925	646.47418	20.24731	24.1420
Totals :				2677.80414	105.84211	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.571	BB	0.3444	327.38226	14.78269	4.9854
2	22.390	BB	0.4912	6239.45117	195.06245	95.0146
Totals :				6566.83344	209.84515	

Figure 2.13 HPLC data for compound **2.9e**

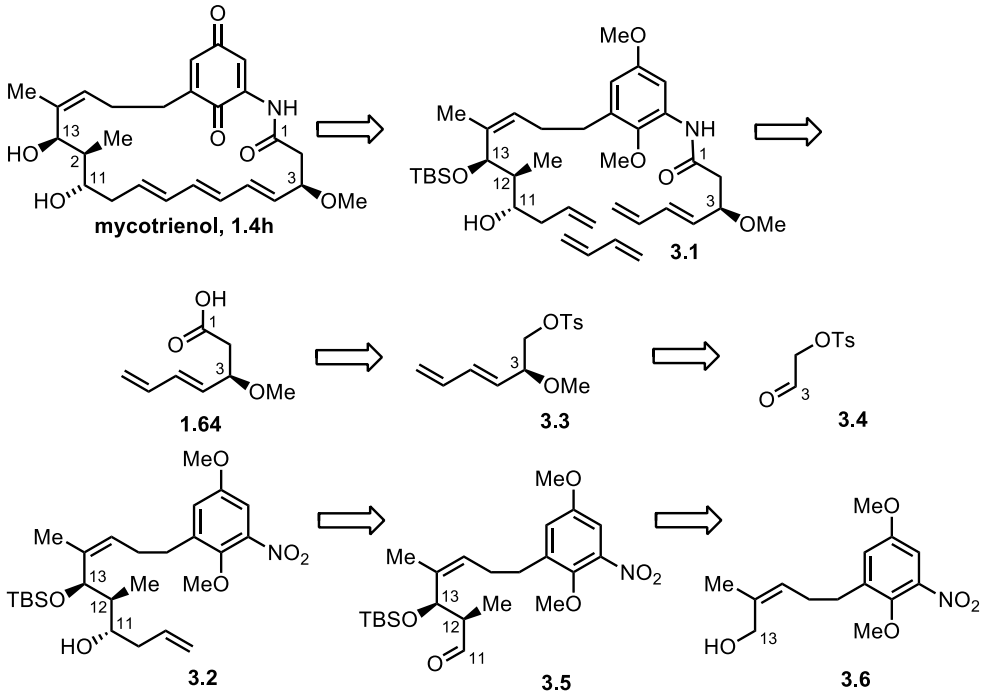
3 STUDIES TOWARD THE SYNTHESIS OF C-17 BENZENE ANSAMYCINS

In the course of a research program dedicated to the development of carbon-carbon bond forming hydrogenations, we recognized the utility of these new methods to quickly synthesize polyketide frameworks relative to traditional methods (chapter 2). We identified mycotrienol (**1.4h**) as our synthetic target, with the aim of demonstrating that C-C bond forming hydrogenations can be used to synthesize a complex molecule more efficiently than traditional methods. Due to the similarity of the C1-C17 ansa chain, a short synthesis of any C-17 benzene ansamycin would by extension allow access to any member of this class of natural products. As a measure of synthetic efficiency, we chose step count to benchmark our synthesis to the prior art.

3.1 Initial efforts toward mycotrienol (1.4h)

For our retrosynthetic analysis, we sought to build on the strategies used in the prior syntheses and use modern metal-catalyzed transformations. With that in mind, our goal was to develop a synthetic route using roughly half the steps as previous syntheses. In order to realize such a dramatic reduction in step count, we planned for two of the key fragments to be synthesized using metal catalyzed C-C bond forming methods developed by Krische and co-workers (Scheme 3.1). Using a modification of an RCM strategy that had been established by Panek[33] and Hayashi,[32] we envisioned a macrocyclization through a butadiene stitching RCM from ene-diene **3.1**. Further disconnection at the C1

amide bond would entail the synthesis of alcohol **3.2** and acid **1.64**, which had been previously prepared by Hayashi and co-workers, in the synthesis of cytotrienin A (**1.6a**) (Scheme 1.17). The synthesis of acid **1.64** could be disconnected to diene **3.3**, which could be constructed with an asymmetric hydrogen-mediated coupling of acetylene with aldehyde **3.4**. Using this method to set the C3 stereochemistry of diene **3.3** and install the diene in one operation would be a distinct advantage in our synthesis.



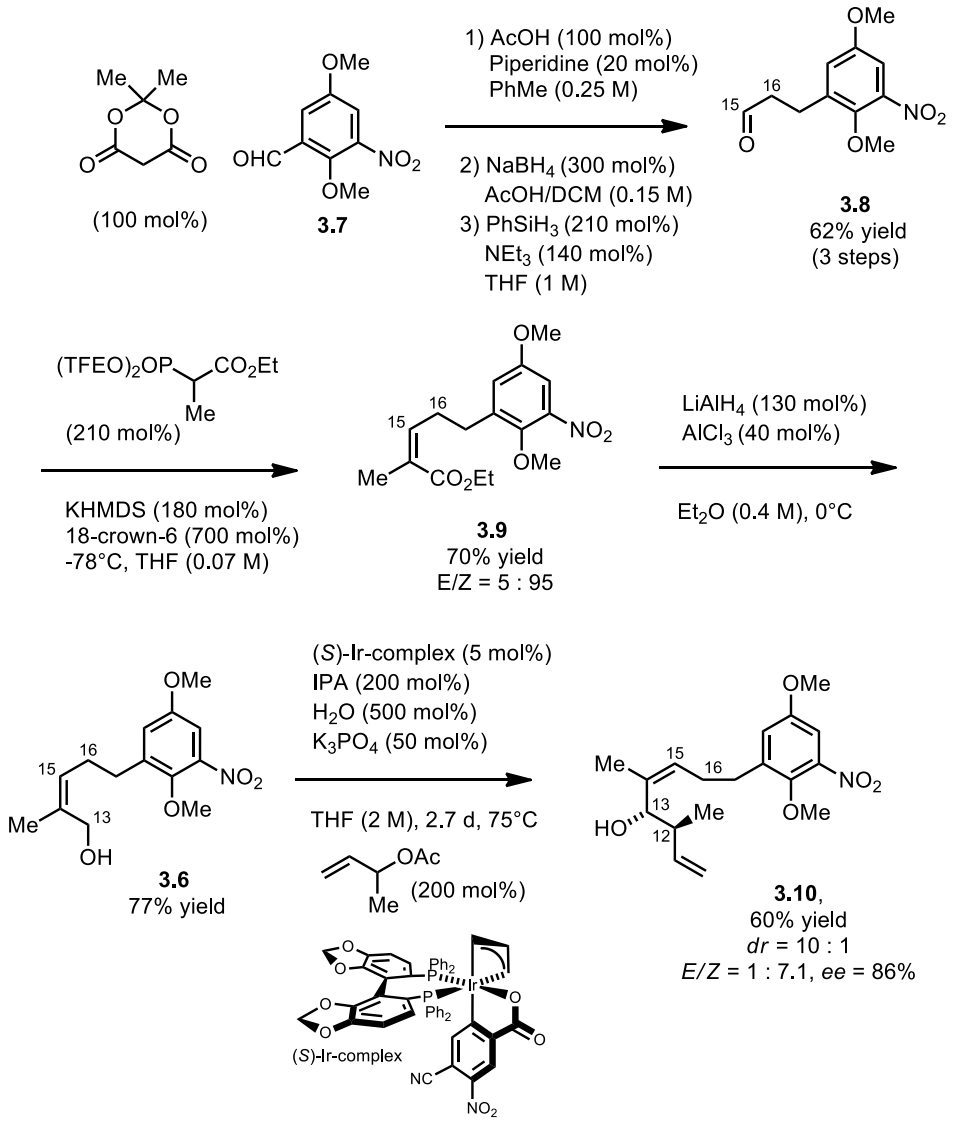
Scheme 3.1 Mycotrienol (**1.4h**) retrosynthesis

Alcohol **3.2** presents a synthetic challenge embodied by three contiguous chiral centers and a (*Z*)-trisubstituted olefin. To construct the stereotriad we envisioned that allylation of aldehyde **3.5** would be used to set the C11 stereochemistry. Aldehyde **3.5** could be prepared via union of allyl alcohol **3.6** with α-methyl allyl acetate under

previously explored iridium-catalyzed crotylation conditions.[78,80,81] Importantly, this methodology would allow for the construction of the C12-C13 stereocenters while avoiding a discreet oxidation of the alcohol to an aldehyde. This might allow aldehyde **3.5** to be synthesized from alcohol **3.6** with *anti*-diastereoselectivity. However, due to limitations in the methodology it would be necessary to invert the C13 stereocenter to access the *syn* isomer found in the natural product.

3.1.1 SYNTHESIS OF ALCOHOL 3.2

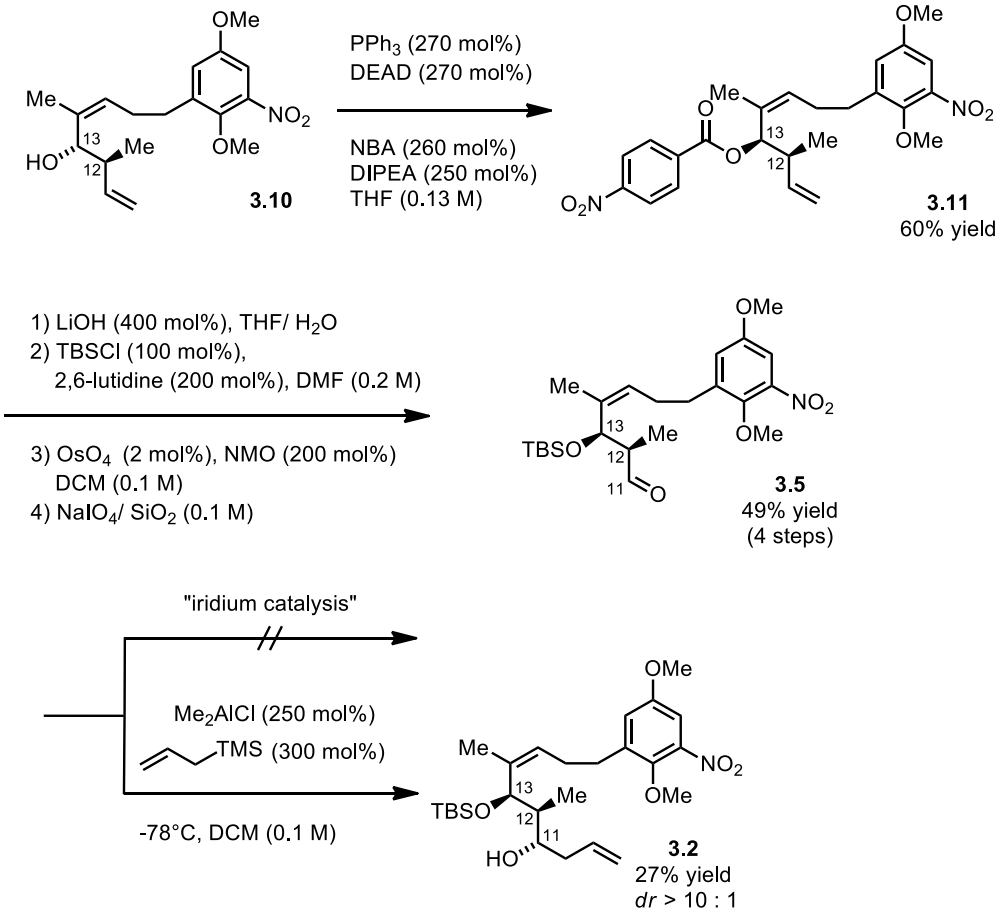
This section describes the contributions by Dr. Michael Rössle that led to initial synthesis of alcohol **3.2**. Beginning with a three step sequence wherein aldehyde **3.7** was transformed to *β*-aryl aldehyde **3.8** using a modification of a known procedure (Scheme 3.2).[110] With *β*-aryl aldehyde **3.8** in hand, the (*Z*)-trisubstituted olefin was installed using the Still-Gennari modification of the Horner-Wadsworth-Emmons reaction delivering enone **3.9** in 70% yield.[111] Alane reduction of the ester functionality provided allylic alcohol **3.6** in 77% yield. Finally, exposure of alcohol **3.6** to the hydrogen-mediated crotylation conditions furnished the desired adduct **3.10** in 60% yield and high selectivity, albeit with significant erosion of the (*Z*)-trisubstituted olefin geometry.



Scheme 3.2 Synthesis of adduct **3.10**

Although adduct **3.10** was formed in good yield, it was an *anti*-selective transformation. To correct this stereochemistry an inversion of the C13 stereocenter was performed using a modification of the Mitsunobu reaction to provide ester **3.11** (Scheme 3.3).[112] The major side product of the reaction was S_N2' addition of the

carboxylate, and was inseparable from the desired product. A four step sequence of ester hydrolysis, protection of C13 alcohol as a TBS ether, selective dihydroxylation, and oxidative cleavage delivered aldehyde **3.5** in 49% yield over four steps. For the installation of the allyl moiety to aldehyde **3.5**, Dr. Rössle originally employed an iridium-catalyzed allylation, but under those reaction conditions the C12 stereocenter was epimerized. This proved to be an insurmountable problem, thus a chelation controlled allylation was investigated. Exposure of aldehyde **3.5** to dimethylaluminum chloride and allyltrimethylsilane delivered stereotriad **3.2** in low yield and good selectivity.[113]



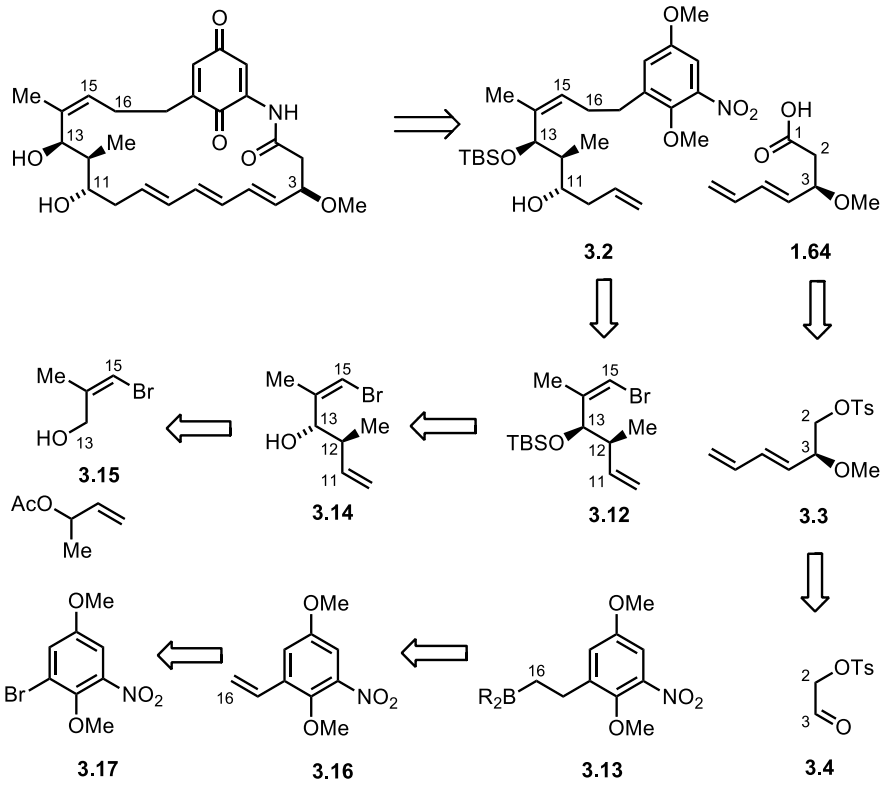
Scheme 3.3 Synthesis of stereotriad **3.2**

In summary, the route developed by Dr. Michael Rössle provided stereotriad **3.2** but there were several issues that had to be addressed: (1) *E*/*Z* isomerization in the allylation of **3.6**, (2) a mixture of S_N2' products in the Mitsunobu inversion of **3.10**, and (3) a low yield in the allylation of **3.5**. To address the *E*/*Z* isomerization and S_N2' problems a new route to aldehyde **3.5** was developed using a Suzuki reaction as a major disconnection.

3.2 Synthetic efforts toward the mycotrienin core

3.2.1 RETROSYNTHESIS

Due to the unsuccessful efforts to construct alcohol **3.2** in sufficient quantity and purity, we revised our strategy to address the challenges of the previous route. We envisioned the C15-C16 bond of alcohol **3.2** would be formed via Suzuki cross-coupling of vinyl bromide **3.12** with borane **3.13** (Scheme 3.4). We also reasoned that side products resulting from the of S_N2' addition in the Mitsunobu reaction associated with the previous route might be suppressed by using *anti*-vinyl bromide **3.14**. To access vinyl bromide **3.14** we would employ our iridium-catalyzed *anti*-crotylation from known alcohol **3.15** and α-methyl allyl acetate. For the other coupling partner in the key Suzuki reaction we planned to access borane **3.13** through a hydroboration of nitro styrene **3.16**, which would be obtained from arene **3.17**.

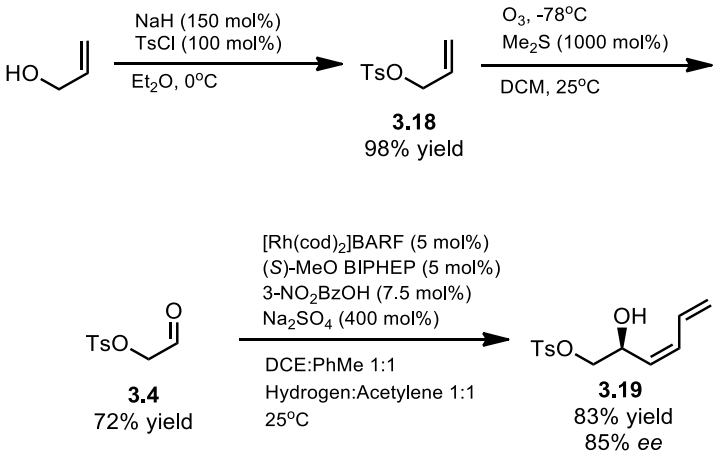


Scheme 3.4 Second generation mycotrienol (**1.4h**) retrosynthesis

3.2.2 ACID FRAGMENT 1.64

Synthesis of acid **1.64** was initially hindered by the inability to find a suitable masked carboxylic acid at the C1 position. The substrate scope for the rhodium-catalyzed dienylation was limited to aldehydes that contained an electron-withdrawing group near the aldehyde (Section 2.2.2). The limitations associated with the narrow substrate scope were circumvented by using aldehyde **3.4** in the dienylation reaction, and constructing the acid in later steps (Scheme 3.5). Treatment of allyl alcohol with sodium hydride and *p*-toluenesulfonyl chloride furnished compound **3**.**18**, which upon exposure to ozone

followed by dimethyl sulfide delivered aldehyde **3.4**. Reaction of aldehyde **3.4** under rhodium-catalyzed dienylation conditions provided (*Z*)-diene **3.19** in 83% yield and 85% *ee* at best. Unfortunately, (*Z*)-diene **3.19** proved to be unstable under the reaction conditions and at ambient temperatures, and thus the yield of the dienylation reaction was difficult to reproduce. Additionally, aldehyde **3.4** was unstable and had to be synthesized and purified immediately prior to use, further increasing the difficulty in obtaining sufficient quantities of (*Z*)-diene **3.19**.

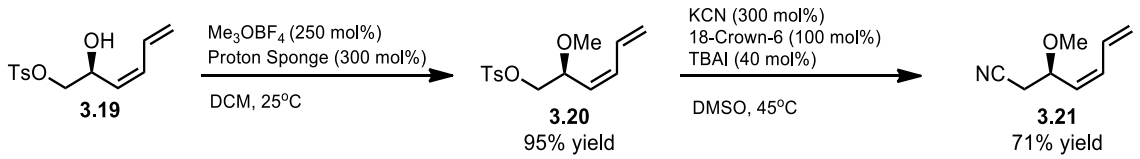


Scheme 3.5 Synthesis of (*Z*)-diene **3.19**

3.2.2.1 Initial route toward acid 1.64

With a route to the diene in place, we sought to install the carboxyl functionality. In initial experiments **3.19** was treated with sodium cyanide, but a mixture of compounds was obtained in all cases. Methylation of the alcohol before cyanide displacement allowed for a simple way to minimize the undesired side reactions. Treatment of compound **3.19** with Meerwein's reagent and proton sponge provided the methyl ether

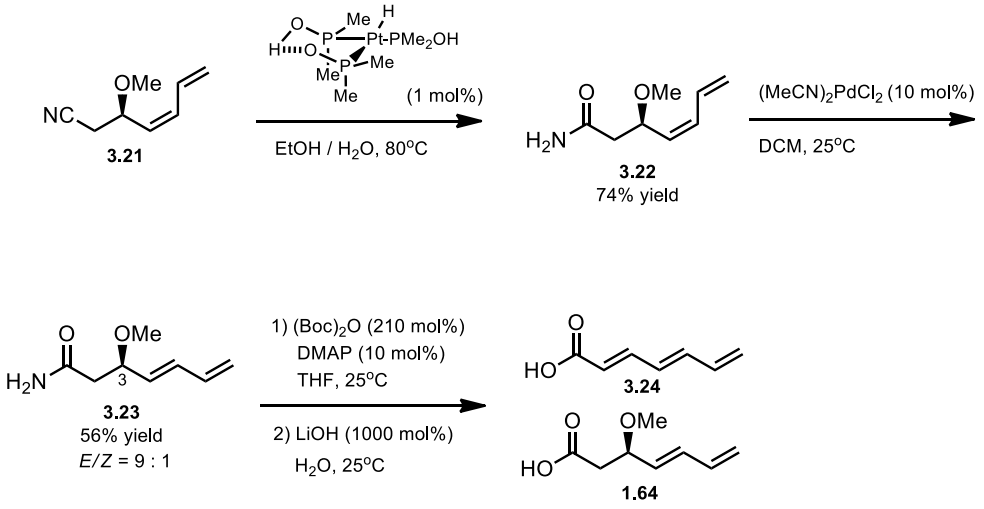
3.20 (Scheme 3.6). We next sought to displace the tosyl alcohol with cyanide, followed by conversion of the resulting nitrile to the desired carboxylic acid. Several cyanide sources, solvents, and additives were investigated but ultimately reaction of **3.20** with potassium cyanide, 18-crown-6 and tetrabutylammonium iodide (TBAI) in DMSO delivered nitrile **3.21** in 71% yield. Control experiments showed that both 18-crown-6 and TBAI were required for the displacement to occur. Additionally, the reaction must be monitored closely, as it was found that at extended reaction times decomposition of nitrile **3.21** occurs.



Scheme 3.6 Synthesis of nitrile **3.21**

Due to the sensitivity of nitrile **3.21** we sought mild conditions for hydration of nitrile to the requiste acid. Treatment of nitrile **3.21** with a homogeneous platinum phosphinito catalyst in an ethanol-water mixture allowed for primary amide **3.22** to be obtained under mild conditions in 74% yield (Scheme 3.7).[114] Our focus then turned to the isomerization of the diene, which was set as an undesired isomer during the rhodium-catalyzed dienylation reaction (Scheme 3.5). Conversion of amide **3.22** from the *Z* to *E* isomer was accomplished with catalytic $PdCl_2(MeCN)_2$,[115] giving the desired (*E*)-olefin **3.23** with a ratio of *E*/*Z* = 9:1 (Scheme 3.7). It is noteworthy that by applying this method, isomerization of the diene took place without migration of the diene. Since we

were aware of the sensitivity of the C3 methyl ether, we sought mild conditions for the hydrolysis of amide **3.23** to acid **1.64**. A two step protocol was used to hydrolyze amide **3.23** by activation of the nitrogen as a leaving group, and subsequent hydrolysis to furnish the carboxylic acid. This procedure did allow access to acid **1.64** but with ~10% of the elimination product **3.24** which proved to be inseparable from the desired compound. Unfortunately, our route to acid **1.64** had a low overall yield and an inseparable side product in the last step, therefore a new route was pursued.

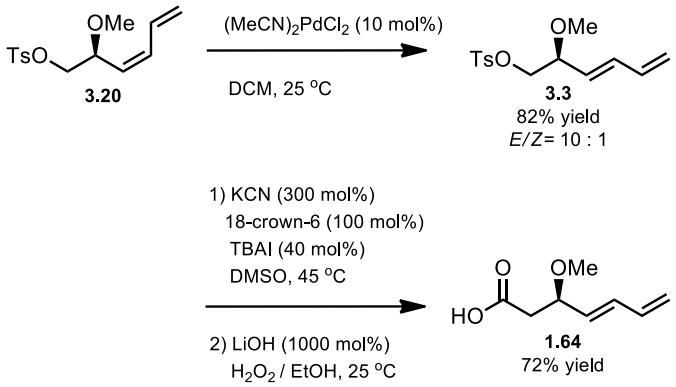


Scheme 3.7 Initial synthesis of acid **1.64**

3.2.2.2 Revised route to acid 1.64

In order to improve the synthesis acid **1.64**, we investigated conditions to convert the nitrile to the carboxylic acid in one step in hopes of avoiding elimination of the C3 methoxy-group. On a model system we found that lithium hydroxide in hydrogen peroxide would allow the hydrolysis to take place. In applying this method to the desired

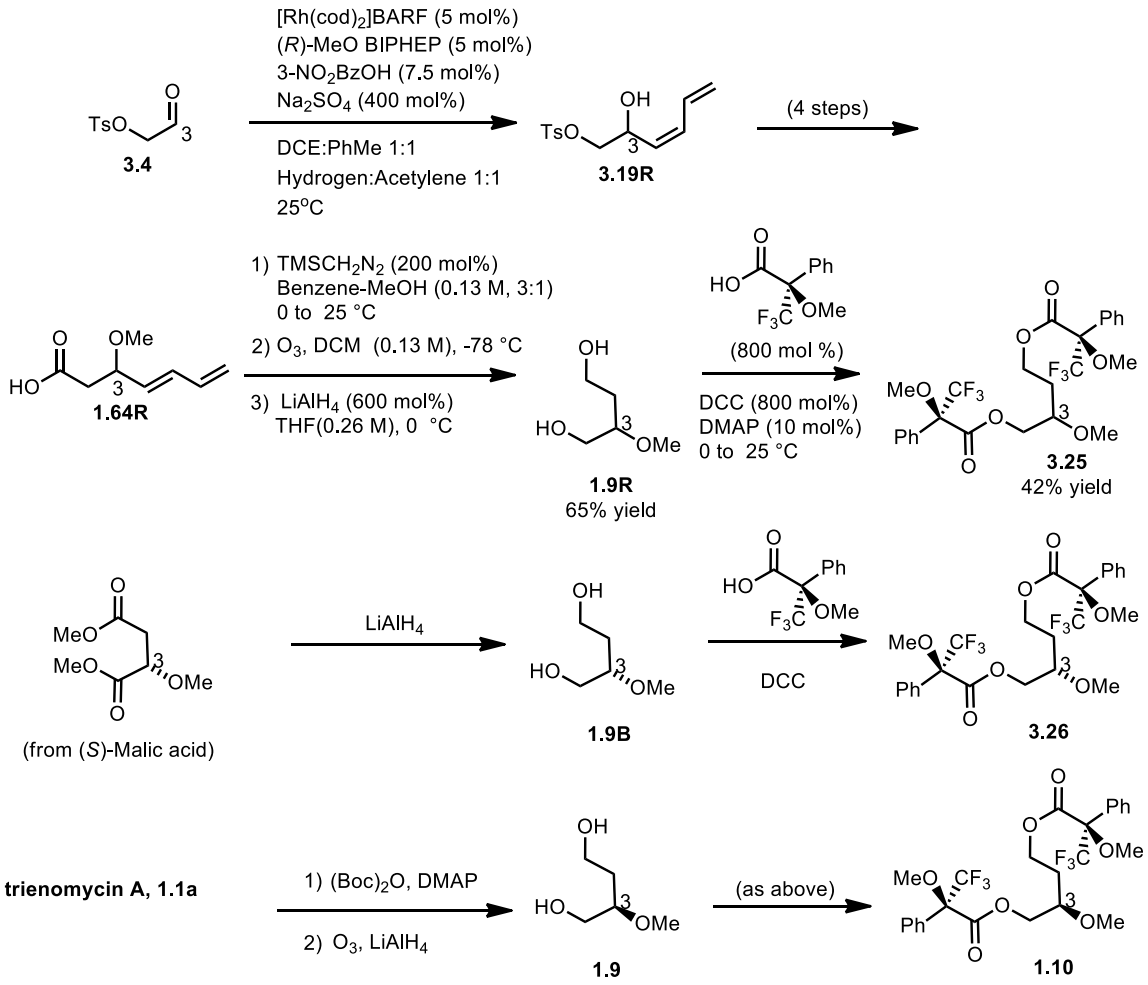
system, the order of operations was changed to permit the isomerization of the (*Z*)-diene **3.20** to give (*E*)-diene **3.3** in 82% yield (Scheme 3.8). Thus, with the diene in the required geometry, compound **3.3** was then treated to conditions previously used to install the nitrile. Due to the high volatility of the nitrile intermediate it was immediately subjected to the conditions of hydrolysis. In this way acid **1.64** was obtained in 72% yield over two steps from diene **3.3**. Our synthesis proceeded in seven steps with 32% overall yield from commercially available material and is shorter than the previous report of this compound, which required 12 steps in 16% overall yield.[32]



Scheme 3.8 Second route to acid **1.64**

3.2.2.3 Absolute stereochemistry confirmation of acid 1.64

During the course of the synthetic work, we needed to confirm the absolute configuration of acid **1.64**. The optical rotation measurement was within the limit of experimental error of the instrument, therefore unreliable. Also, due to an inconsistency in the literature,[52,53] it was not clear which chiral ligand would produce the desired stereochemistry in dienylation of aldehyde **3.4**. To confirm the acid stereochemistry we transformed our acid, synthesized with the (*R*)-MeO-BIPHEP ligand, into a *bis*-Mosher ester and compared to known *bis*-Mosher ester **1.10** (Scheme 3.9). Exposure of acid **1.64R** sequentially to TMS-diazomethane, ozone, and lithium aluminum hydride provided diol **1.9R**, which after esterification with Mosher's acid provided *bis*-Mosher ester **3.25**. Comparsion of the proton NMR spectra of *bis*-Mosher ester **3.25** to the known *bis*-Mosher esters **3.26** and **1.10** indicated that the spectra from **3.25** and **3.26** were identical.[19] Therefore, the acid synthesized from the (*R*)-MeO-BIPHEP ligand led to *bis*-mosher ester with the C3-stereocenter in the (*S*)-configuration. This was opposite to the stereochemistry found in the natural product, consequently the (*S*)-MeO-BIPHEP ligand was used to construct acid **1.64**.

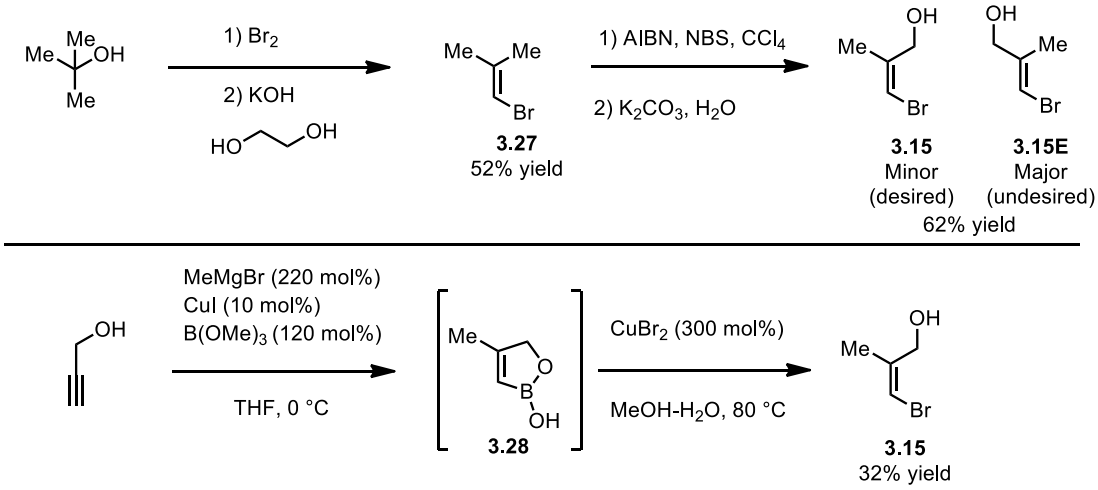


Scheme 3.9 Confirmation of acid **1.64** stereochemistry

3.2.3 REVISED ROUTE FOR ALCOHOL 3.2

With the route to acid **1.64** in place, we turned our attention to a revised synthesis of alcohol **3.2**. Using a known procedure[116] to access vinyl bromide **3.15**, *tert*-butanol was brominated and subsequent elimination provided bromide **3.27** (Scheme 3.10). Radical halogenation of **3.27** followed by hydrolysis provided a mixture of two isomers with the desired (*Z*)-isomer as the minor component. Since we were unable to completely

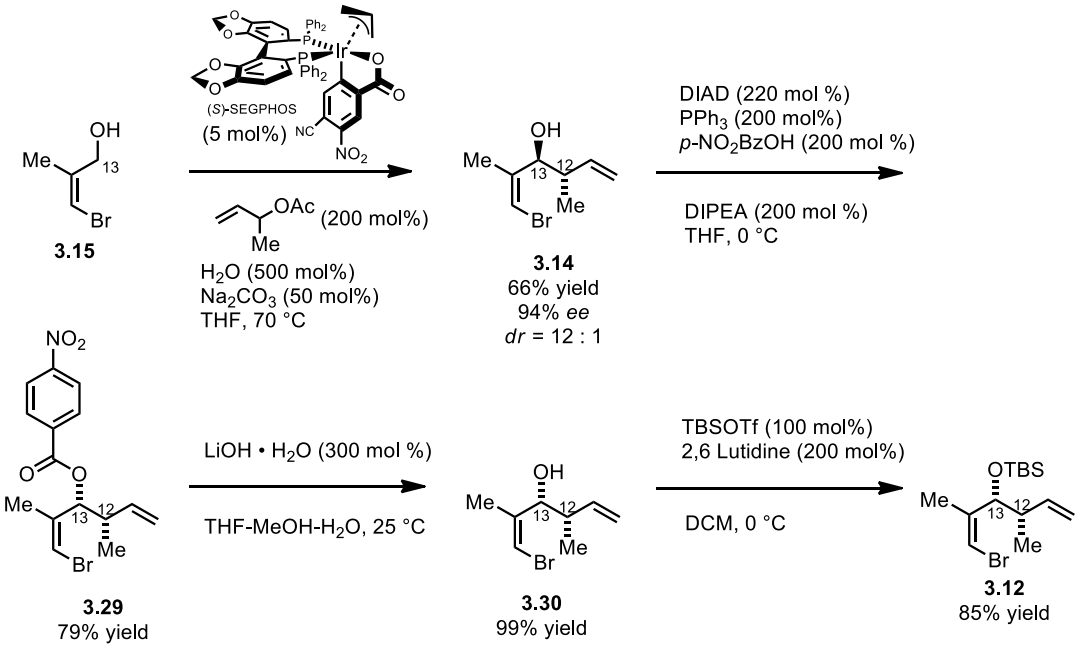
separate the mixture, a method to synthesize vinyl bromide **3.15** as a single isomer was needed. Through an adaptation of a known protocol,[117] propargyl alcohol was transformed into boronate intermediate **3.28**, which was then treated with $CuBr_2$ to furnish vinyl bromide **3.15** as single isomer in 32% yield (Scheme 3.10).



Scheme 3.10 Improved synthesis of vinyl bromide **3.15**

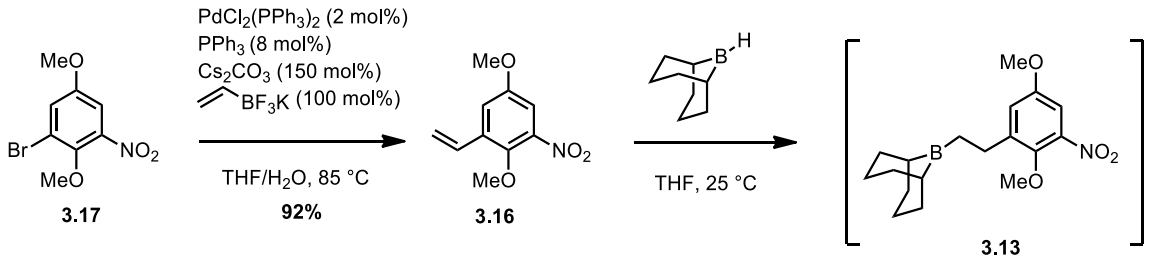
With access to vinyl bromide **3.15**, as a single isomer, we investigated it as a substrate in a C-C bond forming transfer hydrogenation. We found that by employing the preformed (*S*)-Segphos complex in the iridium-catalyzed crotylation allowed compound **3.14** to be obtained in 70% yield with the *anti*-diastereomer as the major product (Scheme 3.11). The relative and absolute stereochemical assignments were inferred based on analogy with the literature precedent.[79] Importantly, this crotylation reaction proceeded without any erosion of the olefin geometry that was observed in the prior route. Inversion of the C13 alcohol under modified Mitsunobu conditions[112] provided ester **3.29**, which was subsequently hydrolyzed to furnish *syn*-alcohol **3.30**. Now that the

stereochemistry at C13-C12 was in the same configuration as in the natural product, the synthesis could continue forward. Exposure of alcohol **3.30** to *tert*-butyldimethylsilyl trifluoromethanesulfonate provided the TBS ether **3.12**. With bromide **3.12** in hand, efforts turned toward the synthesis of borane **3.13**, which was en route to our proposed Suzuki cross-coupling.



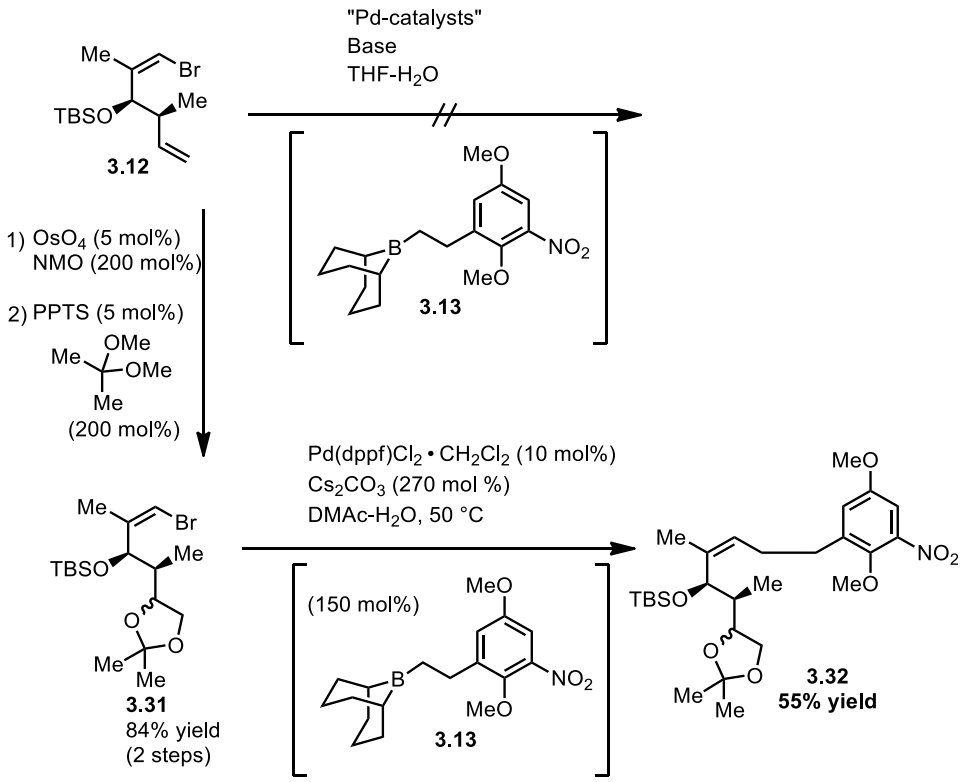
Scheme 3.11 Synthesis of vinyl bromide **3.12**

The synthesis of borane **3.13** began with a Suzuki reaction of commercially available bromide **3.17** and potassium vinyltrifluoroborate to furnish nitro styrene **3.16** (Scheme 3.12). Hydroboration of nitro styrene **3.16** with 9-BBN provided borane **3.13**. This borane adduct was prepared and used without isolation or purification due to the oxygen sensitivity of the borane.



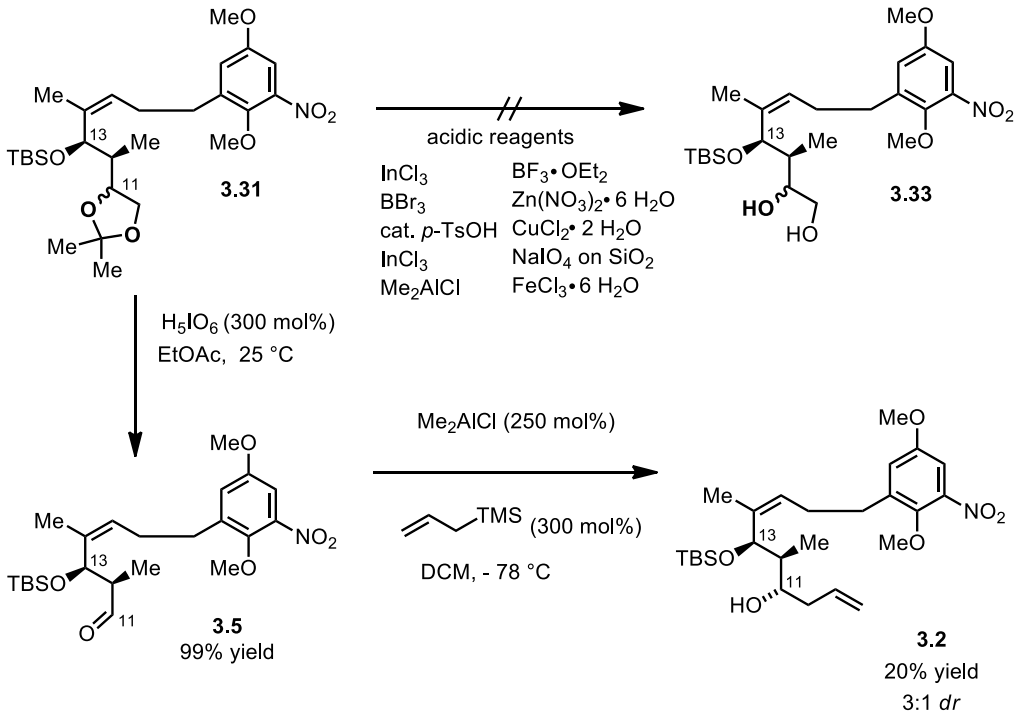
Scheme 3.12 Synthesis of borane **3.13**

Unfortunately vinyl bromide **3.12** was not productive in a Suzuki cross-coupling with borane **3.13** (Scheme 3.13). In model studies, other vinyl and aryl bromides were successfully coupled to borane **3.13**. This difference in reactivity could be attributed to interference from the neighboring olefin on the vinyl bromide **3.12**, which after oxidative addition of palladium might occupy a coordination site on palladium and inhibit the reaction. We sought to test this hypothesis by selectively oxidizing the terminal double bond of **3.12** to remove the possibility of alkene coordination. This was accomplished by a catalytic dihydroxylation followed by subsequent protection of the intermediate diol to furnish acetonide **3.31**. With intermediates **3.31** and **3.13** in hand, we sought to join them through a sp^2-sp^3 Suzuki cross coupling (Scheme 3.13). This proved to be challenging as most conditions provided adduct **3.32** in low yield. After an optimization that examined palladium source, ligand, base, solvent, temperature and time we arrived at the conditions that would give adduct **3.32** in modest yield. With access to suitable quantities of adduct **3.32** in place, it was now possible to determine if the route to **3.2** is viable.



Scheme 3.13 Synthesis of acetonide **3.32**

While investigating conditions for the deprotection of acetonide **3.31** to diol **3.33**, we were unable to deprotect the acetonide while keeping the C13 TBS ether intact (Scheme 3.14). Fortunately, we found that periodic acid[118] would simultaneously deprotect and oxidize the acetonide moiety furnishing aldehyde **3.5** in 99% yield. Unfortunately, the chelation controlled addition of allyltrimethylsilane to aldehyde **3.5** to furnish **3.2** proceeded in just 20% yield and with a 3:1 diastereomeric ratio. At this junction we questioned if a different chelating group at the C13 position would increase the yield and selectivity of the allylation reaction.

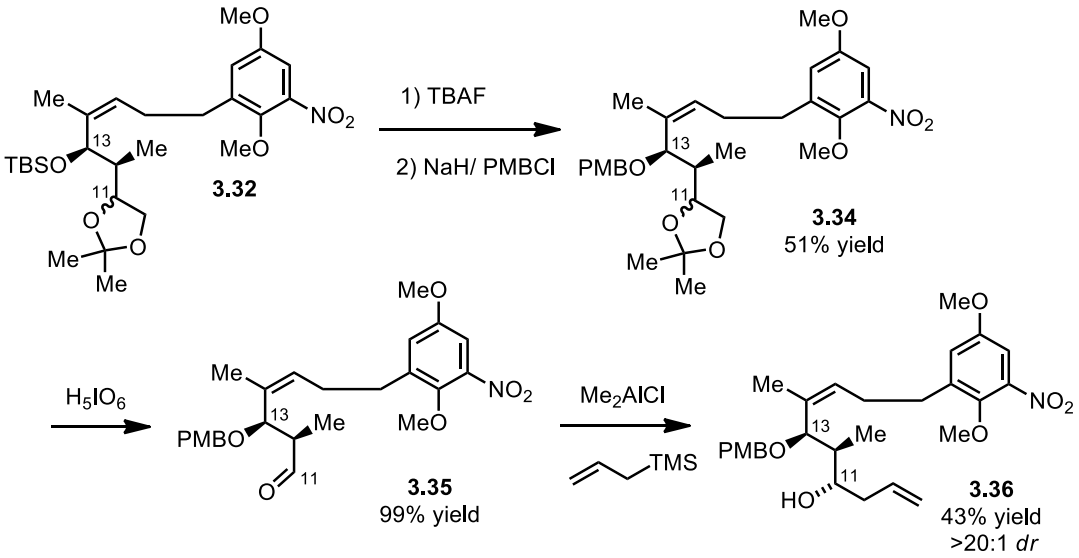


Scheme 3.14 Synthesis of stereotriad **3.2**

3.2.3.1 C13 protecting group swap

We proposed that the chelation controlled addition would be improved by exchanging the C13 TBS ether for a 4-methoxybenzyl (PMB) ether. To this end, silyl deprotection of adduct **3.32** followed by etherification with 4-methoxybenzyl chloride (PMB-Cl) and sodium hydride furnished PMB ether **3.34** (Scheme 3.15). Subsequent oxidative deprotection of the acetonide moiety with periodic acid delivered aldehyde **3.35**. Exposure of aldehyde **3.35** to dimethylaluminum chloride followed by allyltrimethylsilane delivered alcohol **3.36** with excellent selectivity albeit in just 24% yield. While we were able to demonstrate that the PMB ether was able to provide higher levels of selectivity than the TBS ether in the chelation controlled addition of our

system, the protecting group swap went against our goal of developing a short route to the C17-benzene ansamycins by adding additional steps.

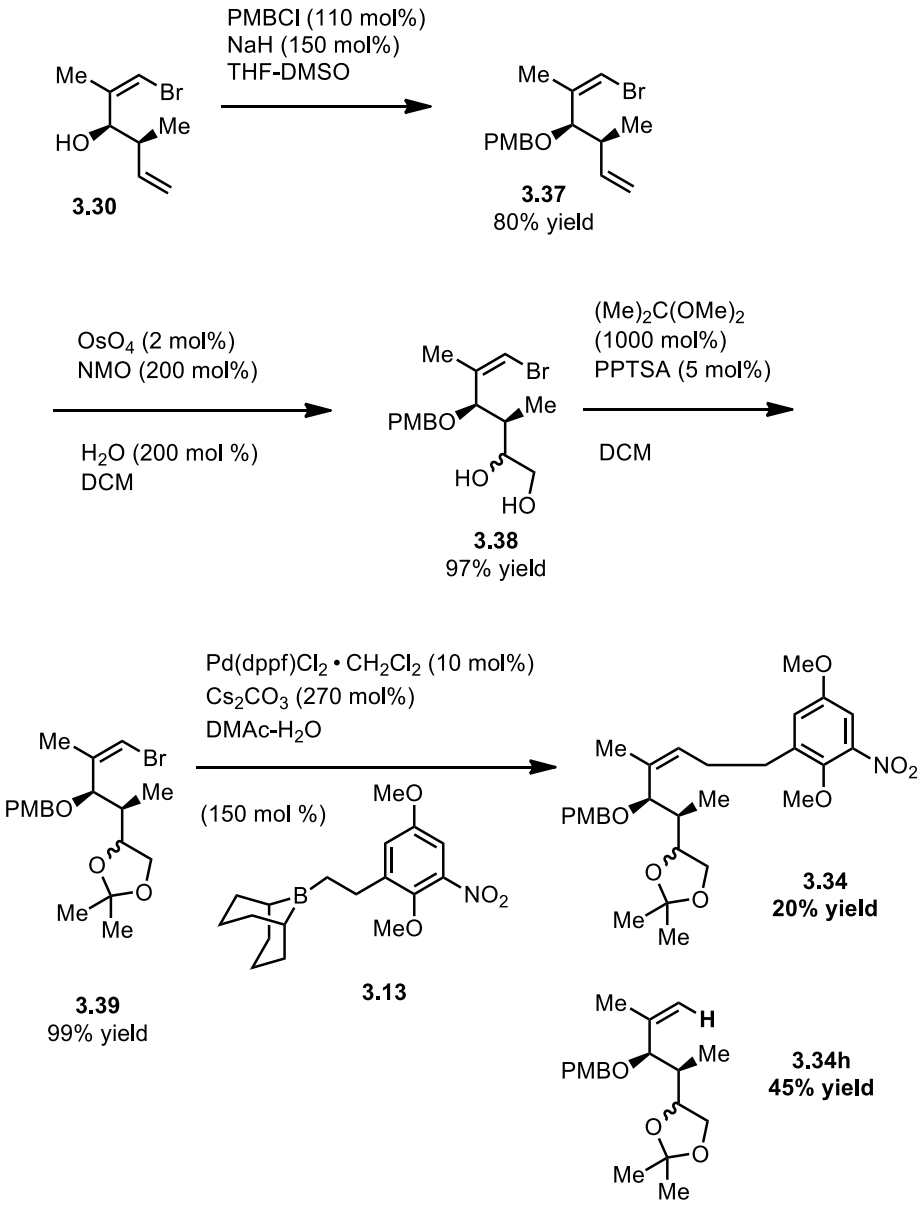


* Sequence preformed by Dr. Michael Rössle

Scheme 3.15 Protecting group swap to synthesize alcohol **3.36**

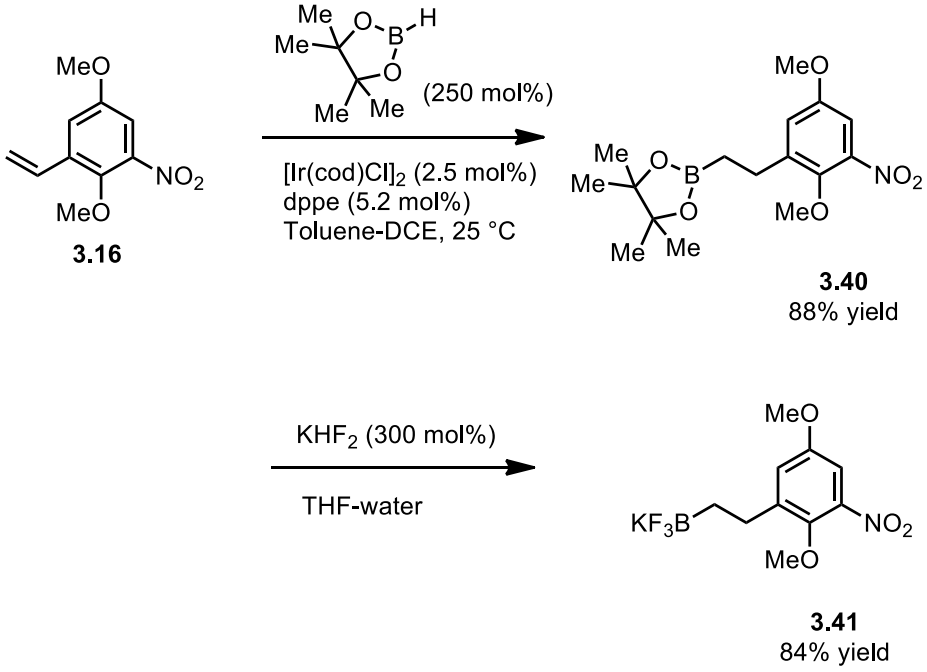
To reduce the step count we revised the route to access alcohol **3.36** without using a protecting group swap. The revised route began at an earlier intermediate; alcohol **3.30** was treated with sodium hydride, tetrabutylammonium iodide, and *p*-methoxy benzyl chloride to furnish *p*-methoxy benzyl ether **3.37** (Scheme 3.16). Selective dihydroxylation of the less substituted olefin of *p*-methoxy benzyl ether **3.37** with catalytic osmium tetraoxide provided diol **3.38**. Acetonide protection of diol **3.38**, proceeded smoothly to provide vinyl bromide **3.39**. Unfortunately, this new coupling partner did not perform well in the Suzuki cross-coupling. The major product arose from the proto-dehalogenation of vinyl bromide **3.39** to give compound **3.34h**. After an

investigation of reaction parameters, the formation of this undesired product was unable to be suppressed.



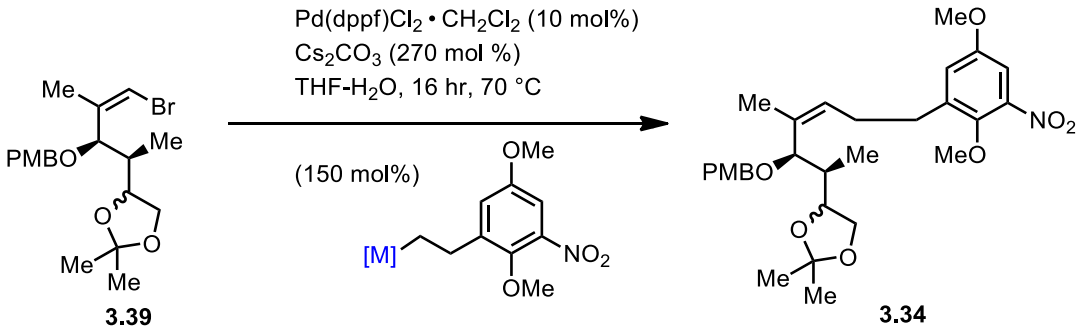
Scheme 3.16 Revised Suzuki coupling route to adduct **3.34**

With few options left to improve the Suzuki reaction, we proposed changing the boron-based coupling partner to a potassium trifluoroborate salt.[119] Regio-selective hydroboration of nitro styrene **3.16** under conditions developed by Miyaura[120] provided pinacol ester **3.40** in 88% yield as a single regioisomer (Scheme 3.17). Exposure of pinacol ester **3.40** to an excess of potassium hydrogen fluoride furnished potassium trifluoroborate salt **3.41** in 84% yield.



Scheme 3.17 Synthesis of pinacol ester **3.40** and trifluoroborate salt **3.41**

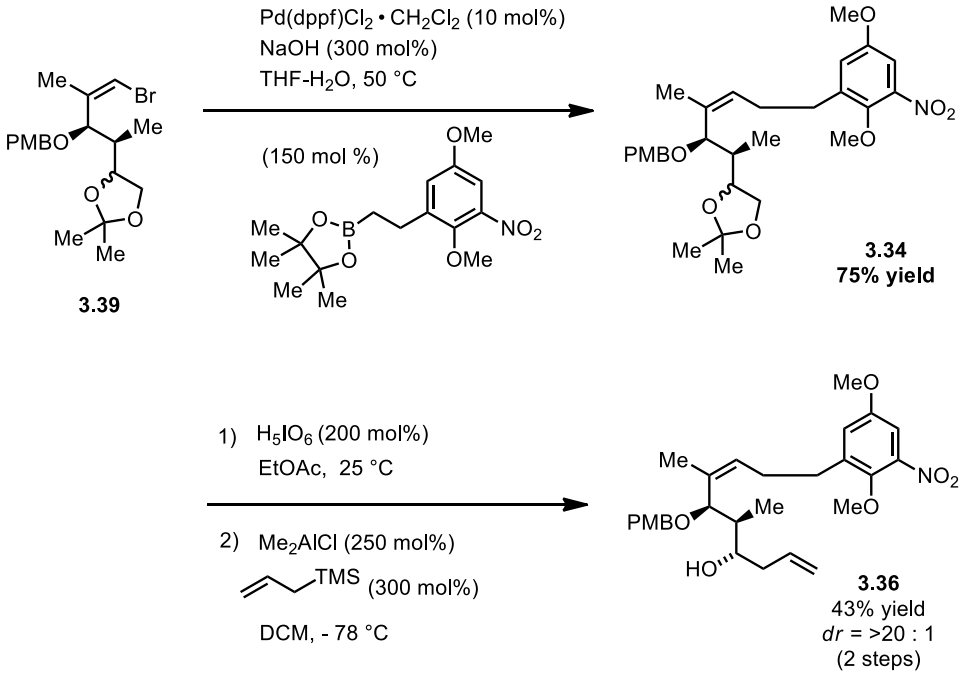
Having secured potassium trifluoroborate salt **3.41,** we investigated the Suzuki coupling to vinyl bromide **3.39**. Conditions optimized for potassium trifluoroborate salt **3.41** were benchmarked against the 9-BBN and pinacol borane derivatives (Scheme 3.18). To our surprise, employing the pinacol ester **3.40** under identical conditions provided adduct **3.34** in 48% yield. After this result we began to explore coupling conditions for pinacol ester **3.40**.



[M]	Yield
9-BBN, **3.13**	20%
KF_3B, **3.41**	40%
B(pin), **3.40**	48%

Scheme 3.18 Comparison of boron coupling partners in Suzuki reaction

We found that by lowering the reaction temperature and substituting cesium carbonate for sodium hydroxide, the Suzuki coupling of vinyl bromide **3.39** and pinacol ester **3.40** provided adduct **3.34** in 75% yield (Scheme 3.19). With this success we were able to avoid the TBS ether protecting group swap (Scheme 3.15) and continue forward with the synthesis to alcohol **3.36**.

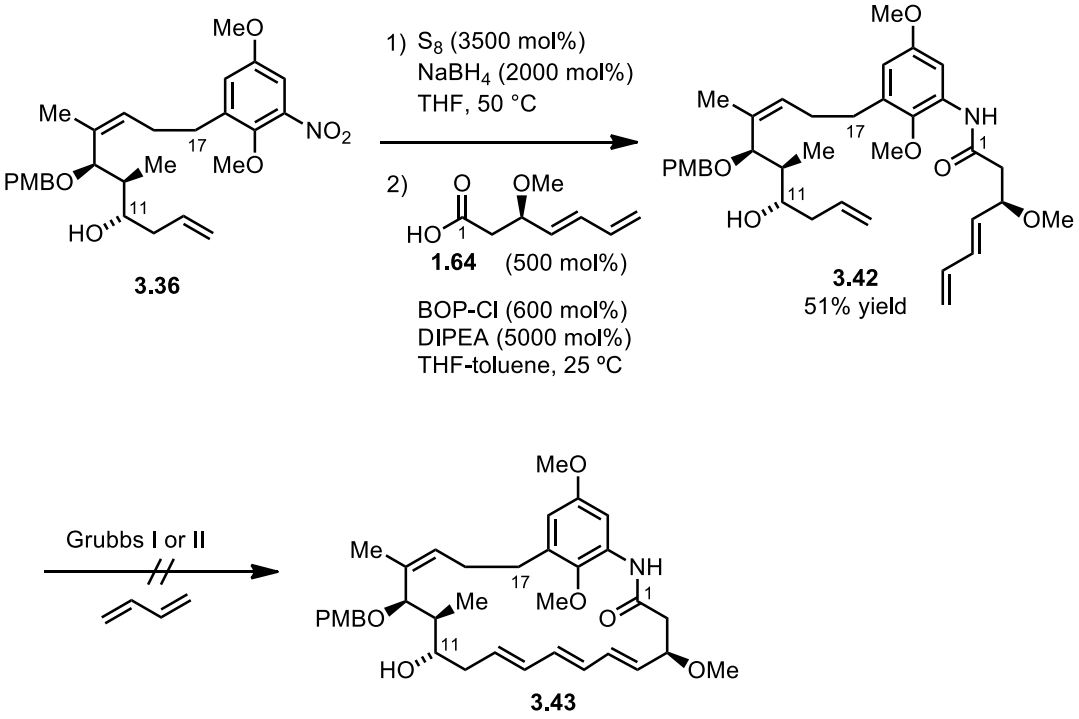


Scheme 3.19 Synthesis of PMB stereotriad **3.36**

3.2.4 FRAGMENT UNION AND RCM

With routes to both alcohol **3.36** and acid **1.64** in place, we investigated their union and subsequent macrocyclization. Selective reduction of nitro moiety of alcohol **3.36** with $NaBH_2S_3$[121] provided an oxygen sensitive aniline that was immediately coupled to acid **1.64** to deliver ene-diene **3.42**. In prior syntheses of C17-benzene ansamycins

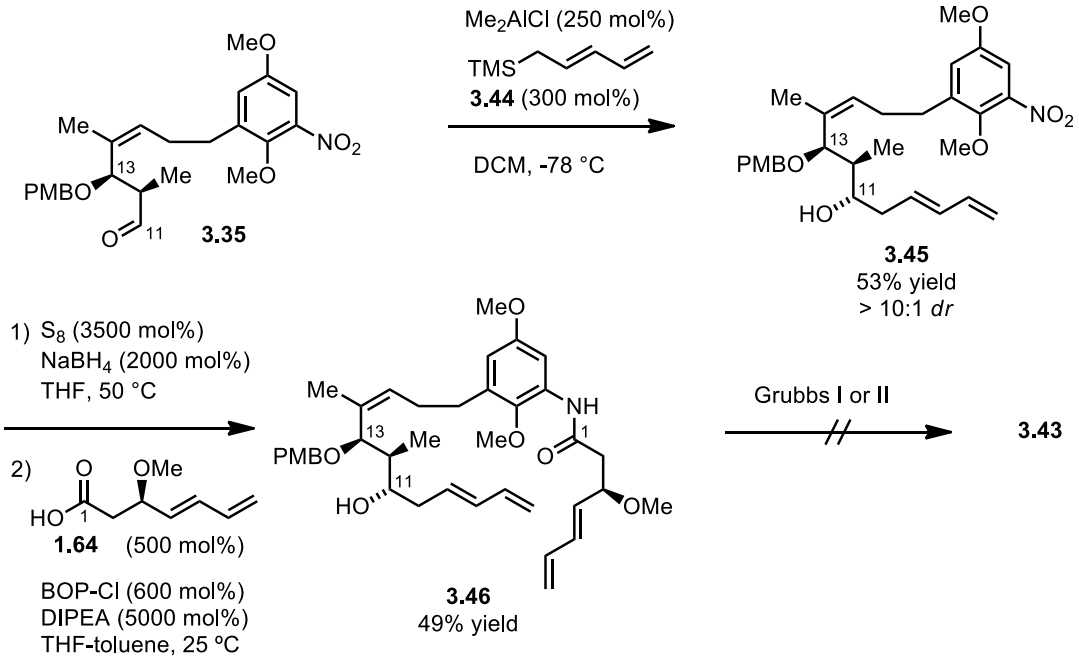
examples of stitching reactions to close the macrocycle and construct the triene moiety were performed by laboratories of Smith (Scheme 1.7) and Panek (Scheme 1.11). We realized an opportunity to investigate a novel stitching RCM in our synthesis with ene-diene **3.42** and butadiene to furnish triene **3.43**. Unfortunately, no RCM products were observed, only unreacted **3.42** was recovered, so we revised our strategy to incorporate a diene-diene RCM.



Scheme 3.20 Initial efforts toward a stitching RCM

In order to construct the target substrate containing two dienes, we returned to aldehyde **3.35** (Scheme 3.21). A modification of our current route allowed us to replace allyltrimethylsilane with a pentadienyl-trimethylsilane[122,123] **3.44** in the chelation

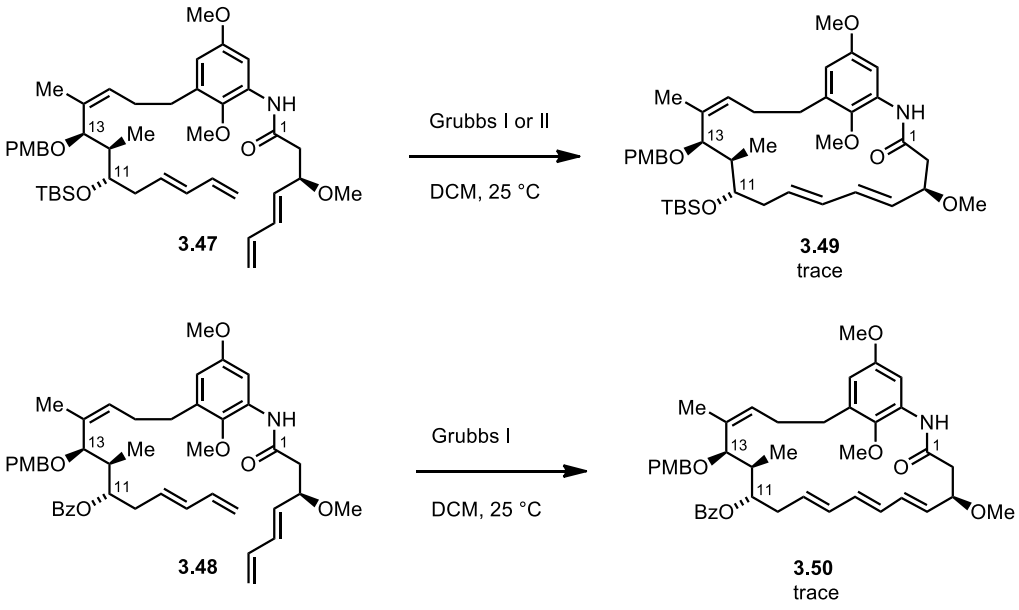
controlled addition permitting access to diene **3.45** in high selectivity and improved yield. Subsequent reduction and coupling to acid **1.64** proceeded efficiently to furnish bis(diene) **3.46**. Unfortunately, exposure of bis(diene) **3.46** to metathesis catalysts did not result in the desired ring-closed product, only unreacted starting material was recovered from the reaction. Prior examples of diene-diene RCM on related systems contained silyl or acyl groups at C11 hydroxyl group. We speculated that the C11 hydroxyl group may be inhibiting the RCM reaction.



Scheme 3.21 Initial efforts toward diene-diene RCM

Our investigation of the diene-diene RCM continued by examining the role of the hydroxyl moiety at the C11 position, accordingly we prepared two additional bis(diene) substrates: TBS bis(diene) **3.47** and benzoate bis(diene) **3.48**. (Scheme 3.22). Exposure of

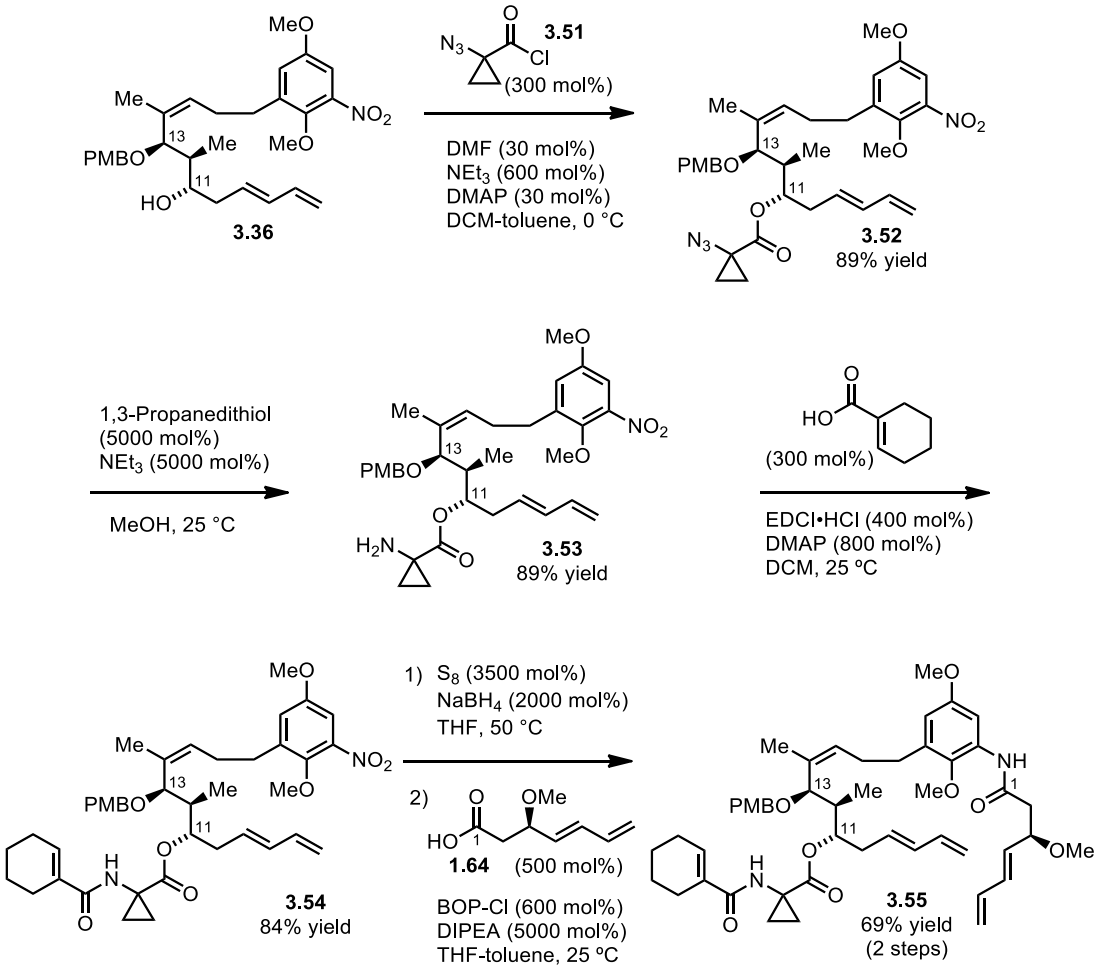
TBS bis(diene) **3.47** to ruthenium based metathesis catalysts provided trace amounts of a ring closure product that was consistent with diene **3.49**. Repeating the study of RCM catalysts with benzoate bis(diene) **3.48**, was more rewarding as trace amounts of RCM product with a mass corresponding to triene **3.50** was obtained. From the experiments conducted it appears that the C11 substituent has an important role in the RCM reaction. Based on this interpretation of the results, we again revised our strategy and target.



Scheme 3.22 Investigation of C11 protecting group in diene-diene RCM

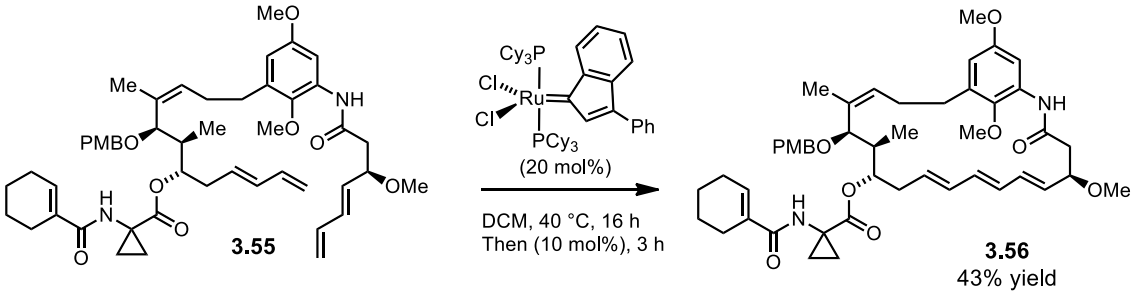
3.3 Synthesis of the cytotrienin A core

The prior success of Hayashi and co-workers (Scheme 1.18) with cytotrienin A (**1.6a**) coupled with our recent experience with a diene-diene RCM led us to investigate the cyclopropylamino acid chain at C11 (Scheme 3.23). Elaboration of the side chain began with esterification of alcohol **3.36** with acid chloride **3.51** to furnish azide **3.52**. Selective reduction of the azide **3.52** with 1,3 propanedithiol provided amine **3.53** without reduction of the nitro group.[32] Amide bond coupling of amine **3.53** and cyclohexene carboxylic acid delivered amide **3.54**. Reduction of the nitro group and acylation of the resulting aniline with acid **1.64** afforded bis(diene) **3.55**.



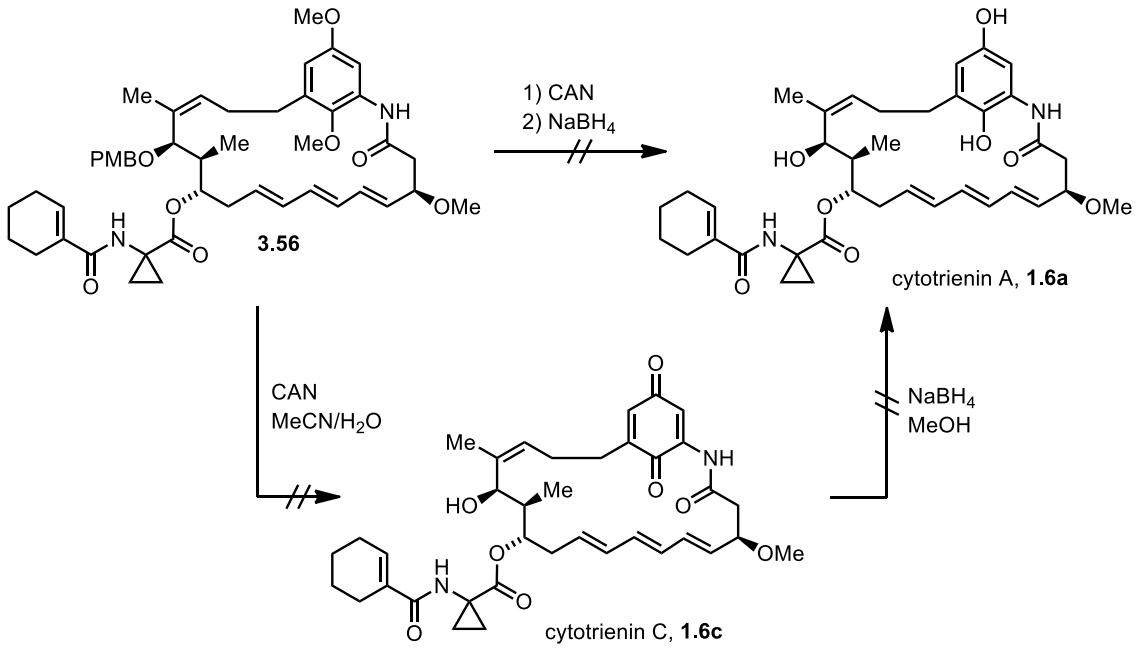
Scheme 3.23 Synthesis of bis(diene) **3.55**

Finally, we were able to investigate the diene-diene RCM with the actual cytotrienin A (**1.6a**) side chain. Thus, using the indenylidene analogue of the first generation Grubbs' metathesis catalyst[124] bis(diene) **3.55** was converted to the cytotrienin A core **3.56** in 43% yield (Scheme 3.24).[125]



Scheme 3.24 Synthesis of the cytotrienin A core **3.56**

With the cytotrienin A core **3.56** in hand, access to the natural product would be possible after a deprotection of the methyl and PMB ether. On a related system Panek and co-workers employed a late stage deprotection of aryl-methyl ethers with ceric ammonium nitrate (CAN) to gain access to the mycotrienins (Scheme 1.11). Since CAN might also cleave PMB ethers we attempted a global ether deprotection (Scheme 3.25). Unfortunately, our efforts were not successful; a variety of Lewis and Brønsted acids were ineffective in a late state cleavage of the protecting groups. On a model system and some of the earlier intermediates the PMB and methyl ethers could be cleaved, but those conditions failed to work on the cytotrienin A core **3.56**.



Scheme 3.25 Efforts to deprotect the cytotrienin A core **3.56**

3.4 Conclusions

In summary, we developed an approach to the C17-benzene triene-ansamycins, as demonstrated by the synthesis of the cytotrienin A core in 17 steps (LLS) from alcohol **3.15**. The synthesis successfully incorporated metal catalyzed C-C bond hydrogenations in the construction of acid **1.64** and stereotriad **3.36**. In a departure from all prior syntheses the C16-C17 bond was made using a Suzuki cross-coupling. This study served as a prelude to a second-generation route, which incorporated a *syn*-diastereo- and enantioselective carbonyl crotylation and the use of a protecting group strategy amenable to late-stage cleavage.

3.5 Experimental

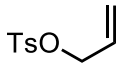
General Methods

All reactions were run under an atmosphere of argon under anhydrous conditions unless otherwise indicated. Dichloromethane (DCM), 1,2-dichloroethane (DCE), tetrahydrofuran (THF), and toluene (PhMe) were obtained from a Pure-Solv MD-5 Solvent Purification System (Innovative Technology, inc). Anhydrous solvents were transferred using oven-dried syringes. All other commercial reagents were used directly without further purification. Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F254). Visualization of the chromatograms was accomplished using UV light and vanillin, anisaldehyde, permanganate, or cerium molybdate stain with heating. Preparative column chromatography using silica gel was performed according to the method of Still.[126] Infrared spectra were recorded on a Nicolet 380 FTIR. Analytical high performance liquid chromatography (HPLC) spectra were obtained using an Agilent Technologies 1200 series HPLC. Analytical Gas Chromatography (GC) spectra were obtained using an Agilent Technologies 7890A GC system. High-resolution mass spectra (HRMS) were obtained on a Waters Micromass Autospec or a Varian FTICR as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+1, M or M–1) or a suitable fragment ion. Melting points were obtained on a Stuart® melting point apparatus SMP3. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded with a Varian spectrometer (400 MHz or 500 MHz) and reported in parts per million (ppm) referenced

to the residual protio solvent signal as an internal standard. Coupling constants are reported in hertz (Hz). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded with a Varian spectrometer (100 MHz or 125 MHz) and reported in parts per million (ppm) referenced to the residual solvent signal as an internal standard. Optical rotations were measured on an ATAGO AP-300 automatic polarimeter at a path length of 1 dm.

Preparation of (*S*)-Ir-complex

To a mixture of $[Ir(cod)Cl]_2$ (520 mg, 0.774 mmol, 100 mol%), (*S*)-SEGPHOS (945 mg, 1.55 mmol, 200 mol %), Cs_2CO_3 (1.010 g, 3.10 mmol, 400 mol %), 4-CN-3-NO_2BzOH (595 mg, 3.10 mmol, 400 mol %) and allyl acetate (387 mg, 3.87 mmol, 500 mol %) in a sealed tube under a N_2 atmosphere was added THF (15.5 mL, 0.05 M). The reaction mixture was stirred for 30 min at 70 °C and heated for 1.5 h at 80 °C, at which point the reaction mixture was allowed to cool to 25 ºC. The reaction mixture was filtered and the filter cake was washed with THF (100 mL). The filtrate was concentrated *in vacuo* and hexanes (350 mL) were added. The title compound was formed as a yellow precipitate, which was collected by filtration and dried under vacuum (1.52 g, 1.47 mmol, 95% yield).



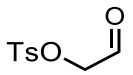
Allyl 4-methylbenzenesulfonate (3.18)

The following procedure is a modification of the prior report[127], which allowed the title compound to prepared in higher yield. To a suspension of sodium hydride (60% in mineral oil, 2.5 g, 65 mmol) and ether (65 mL) under an atmosphere of argon was added allyl alcohol (2.9 mL, 43 mmol) at ambient temperature. After gas evolution ceased the reaction mixture was cooled to 0 °C. *p*-Toluenesulfonyl chloride (8.1 g, 43 mmol) was dissolved in ether (100 mL) and resulting solution was added dropwise to reaction mixture. After the addition was complete the reaction mixture was warmed to ambient temperature and allowed to stir for 1 h. The reaction mixture was added to an aqueous solution of ammonium chloride (100 mL). The resulting mixture was extracted with ether (3 x 50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting oil was washed with hexanes (2 x 20 mL) and concentrated under reduced pressure to give allyl 4-methylbenzenesulfonate (9.0 g, 42 mmol, 98% yield) as a clear oil. The data for the compound was consistent with reported values.[127]

R_f (SiO_2, hexanes/EtOAc = 9 : 1) = 0.6.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 5.78 (ddt, *J* = 17.1 Hz, 10.4 Hz, 5.9 Hz, 1H), 5.31–5.19 (m, 2H), 4.49 (ddd, *J* = 5.9 Hz, 1.5 Hz, 1.2 Hz, 2H), 2.41 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.89, 133.07, 130.19, 129.86, 127.83, 120.21, 70.81, 21.58 ppm.

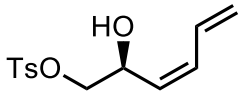


2-Oxoethyl 4-methylbenzenesulfonate (3.4)

The following procedure is a modification of the prior report[128], which allowed the title compound to prepared in higher yield A solution of allyl 4–methylbenzenesulfonate (3.1 g, 15 mmol) in dichloromethane (140 mL) at –78 °C was sparged with ozone until the reaction mixture was pale blue. Ozone was removed and the reaction was sparged with argon for 5 min. Dimethyl sulfide (10.0 mL, 142 mmol) was added at –78 °C and reaction was allowed to warm to ambient temperature with stirring for 12 h. The reaction mixture was concentrated under reduced pressure and purified (SiO_2, 30% to 70% ethyl acetate/hexanes, gradient elution) to give 2–oxoethyl 4–methylbenzenesulfonate (2.25 g, 8.20 mmol, 72 % yield) as a light yellow oil. Due to the rapid decomposition of the title compound, it was stored as a 0.2 M solution in toluene at –20 °C. The data for the title compound was consistent with reported values.[128]

R_f (SiO_2, hexanes/EtOAc = 1 : 2) = 0.2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (s, 1H), 7.82–7.79 (m, 2H), 7.38–7.35 (m, 2H), 4.50 (s, 2H), 2.45 (s, 3H) ppm.



(*S*,*Z*)-2-Hydroxyhexa-3,5-dienyl 4-methylbenzenesulfonate (3.19)

To a solution of $[Rh(COD)_2]BARF$ (155 mg, 0.13 mmol), (*S*)-MeO-BIPHEP (72 mg, 0.13 mmol), 3-nitrobenzoic acid (39 mg, 0.20 mmol), and Na_2SO_4 (1.85 g, 13.1 mmol) in 1,2-dichloroethane (11 mL) and toluene (11 mL) under an atmosphere of hydrogen and acetylene gas (approximately 1:1 by volume) was added a solution of 2-oxoethyl 4-methylbenzenesulfonate (700 mg, 3.27 mmol) in 1,2-dichloroethane (3.5 mL) and toluene (3.5 mL). The resulting mixture was stirred at ambient temperature for 16 h. The crude reaction mixture was filtered, concentrated under reduced pressure, and purified (SiO_2, 30% ethyl acetate/hexanes) to give (*S*,*Z*)-2-hydroxyhexa-3,5-dienyl 4-methylbenzenesulfonate (729 mg, 2.71 mmol, 83% yield) as a colorless oil. The resulting compound was not stable as a neat oil at –20 ºC. The stereochemical assignment was inferred based on analogy with the literature precedent.[52]

R_f (SiO_2, hexanes/EtOAc = 2 : 1) = 0.5.

$[\alpha]_{24}^{D}$= +106 (*c* = 0.65, $CHCl_3$, 85% *ee*).

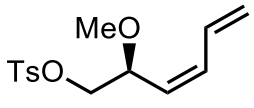
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.49–6.39 (m, 1H), 6.02 (t, *J* = 11.1 Hz, 1H), 5.26–5.12 (m, 3H), 4.75 (s, 1H), 3.90 (dd, *J* = 8.0 Hz, 5.7 Hz, 2H), 3.18 (s, 1H), 2.37 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 133.0, 132.5, 131.2 (3), 129.9 (2), 127.9, 120.7, 72.9, 66.0, 21.6 ppm.

FTIR (Neat): λ^{-1} = 1354, 1172, 1095 cm^{-1}.

HRMS (CI): Calcd. for $C_{13}H_{16}O_4S$ (M): 268.0769, found 268.0765.

HPLC (Chiralcel OD–H column, 3% *i*-PrOH/hexanes, 1 mL/min, 230 nm), t_{minor} = 11.1 min, t_{major} = 13.3 min; *ee* = 85%.



(*S*,*Z*)–2–Methoxyhexa–3,5–dienyl 4–methylbenzenesulfonate (3.20)

To a solution of (*S*,*Z*)-2-hydroxyhexa-3,5-dienyl 4-methylbenzenesulfonate (330 mg, 1.23 mmol) in dichloromethane (25 mL) at ambient temperature under an atmosphere of argon was added trimethyloxonium tetrafluoroborate (455 mg, 3.08 mmol) and 1,8-bis(dimethylamino)naphthalene (791 mg, 3.69 mmol). The resulting mixture was stirred for 2 h at ambient temperature. The crude reaction mixture was filtered, concentrated under reduced pressure, and purified (SiO_2, 10% ethyl acetate/hexanes) to give (*S*,*Z*)-2-methoxyhexa-3,5-dienyl 4-methylbenzenesulfonate (330 mg, 1.17, 95% yield) as a clear oil.

R_f (SiO_2, hexanes/EtOAc = 2 : 1) = 0.8.

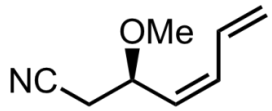
$[\alpha]_{26}^{D}$= +78 (*c* = 1.0, $CHCl_3$, 85% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89–7.30 (m, 2H), 7.46–7.30 (m, 2H), 6.54 (dt, *J* = 16.8 Hz, 10.5 Hz, 1H), 6.23 (t, *J* = 11.3 Hz, 1H), 5.30–5.26 (m, 2H), 5.16 (t, *J* = 10.0 Hz, 1H), 4.33 (dt, *J* = 9.0 Hz, 5.7 Hz, 1H), 4.00–3.98 (m, 2H), 3.24 (s, 3H), 2.44 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8, 134.9, 132.9, 131.0, 129.8 (3), 127.9 (2), 126.2, 121.0, 74.6, 56.5, 21.6 ppm.

FTIR (Neat): λ^{-1} = 1359, 1188, 1174, 1096 cm^{-1}.

HRMS (CI): Calcd. for $C_{14}H_{18}O_4S$ (M): 282.0926, found 282.0924.



(*R*,*Z*)-3-Methoxyhepta-4,6-dienenitrile (3.21)

To a solution of **3.20** (299 mg, 1.06 mmol), 18-crown-6 (280 mg, 1.06 mmol), tetrabutylammonium iodide (80 mg, 0.21 mmol) in dimethylsulfoxide (0.5 ml) was added potassium cyanide (300 mg, 3.18 mmol) and stirred at 45 ^oC for 90 min. The crude reaction mixture was added to ethyl acetate (50 mL) and washed with brine (2 x 100 mL). The organic extract was dried over sodium sulfate, filtered, concentrated under reduced pressure and purified (SiO_2, 10% ether/hexanes) to give **3.21** (103 mg, 71%yield) as a light yellow oil.

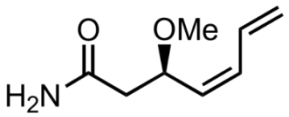
$[\alpha]_{25}^{D}$= 7.5 (*c* = 0.9, $CHCl_3$).

^{1}H NMR (400 MHz; $CDCl_3$) δ 6.60-6.51 (m, 1H), 6.28-6.22 (m, 1H), 5.33-5.28 (m, 1H), 5.26-5.22 (m, 2H), 4.33 (dtd, *J* = 9.2 Hz, 6.0 Hz, 1.0 Hz, 1H), 3.25 (s, 3H), 2.51 (dd, *J* = 6.0 Hz, 1.4 Hz, 2H).

^{13}C NMR (100 MHz; $CDCl_3$) δ 134.9, 130.8, 128.3, 121.4, 117.2, 72.0, 56.7, 24.7.

FTIR (Neat): λ^{-1} = 2230, 1359, 1188, 1174, 1096 cm^{-1}.

HRMS calcd. for $C_8H_{12}NO$ (M+H): 138.0919, found 138.0925.



(*R*,*Z*)-3-Methoxyhepta-4,6-dienamide (3.22)

To **3.21** (120 mg, 0.876 mmol) and hydrido(dimethylphosphinous acid)[hydrogen bis(dimethylphosphinito)]platinum[114] (1.9 mg, 0.0044 mmol) under an atmosphere of argon was added a solution of ethanol (2 mL) and water (1 mL). The resulting mixture was stirred at 80 ^{o}C for 15 h. The crude reaction mixture was extracted with dichloromethane (3 x 20 mL). The organic extracts were combined, concentrated under reduced pressure, and purified (SiO_2, 2% ethanol/ethyl acetate) to give **3.22** (99 mg, 74% yield) as a clear oil.

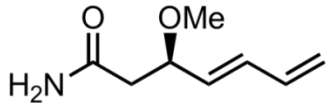
$[\alpha]_{25}^{D}$ = 9.5 (*c* = 0.40, $CHCl_3$).

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.68-6.58 (m, 1H), 6.40 (s, 1H), 6.17 (t, *J*= 11.2 Hz, 1H), 6.11 (s, 1H), 5.28-5.17 (m, 3H), 4.51-4.45 (m, 1H), 3.26 (s, 3H), 2.48-2.29 (m, 2H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 173.5, 133.3, 131.4, 130.5, 120.5, 73.6, 56.5, 42.5.

IR(neat): λ^{-1} 3135, 2928, 1673, 1397, 1217, 1093, 999, 915, 748, 665.

HRMS calcd. for $C_8H_{14}NO_2$ (M+H): 156.1025, found 156.1026



(*R*,*E*)-3-Methoxyhepta-4,6-dienamide (3.23)

To a solution of **3.22** (134 mg, 0.876 mmol) in dichloromethane (1.6 mL) under an atmosphere of argon was added $PdCl_2(MeCN)_2$ (10 mg, 0.087 mmol), the resulting mixture was stirred for 18 h at ambient temperature. The crude reaction mixture was concentrated under reduced pressure and purified (SiO_2, 5% isopropanol/chloroform) to give **3.23** (75 mg, 56%, *E*/*Z* = 9:1) as a clear oil

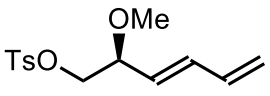
$[\alpha]_{27}^{D}$= -50.3 (*c* = 0.35, $CHCl_3$).

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.37-6.22 (m, 3H), 5.65 (s, 1H), 5.55 (dd, *J* = 14.8 Hz, 7.9 Hz, 1H), 5.25 (dd, *J* = 16.5 Hz, 2.1 Hz, 1H), 5.16-5.13 (m, 1H), 4.03-3.98 (m, 1H), 3.30 (s, 3H), 2.47-2.43 (m, 2H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 173.5, 136.0, 134.1, 132.0, 118.8, 78.7, 56.6, 42.5.

IR(neat): λ^{-1} 3338, 3197, 1662, 1401, 1089, 1003, 955, 906.

MS calcd. for $C_8H_{14}NO_2$ (M+H): 156.1, found 156.1



(*S*,*E*)–2–Methoxyhexa–3,5–dienyl 4–methylbenzenesulfonate (3.3)

To a solution of (*S*,*Z*)-2-methoxyhexa-3,5-dienyl 4-methylbenzenesulfonate (512 mg, 1.82 mmol) in dichloromethane (3.6 mL) under an atmosphere of argon was added $PdCl_2(MeCN)_2$ (55 mg, 0.36 mmol), the resulting mixture was stirred for 5 days at ambient temperature. The crude reaction mixture was diluted with diethyl ether (30 mol), filtered, concentrated under reduced pressure, and purified (SiO_2, 10–30% ether/hexanes, gradient elution) to give (*S*,*E*)-2-methoxyhexa-3,5-dienyl 4-methylbenzenesulfonate **3.3** (398 mg, 1.41 mmol, 78% yield) as a light yellow oil.

R_f (SiO_2, hexanes/EtOAc = 2 : 1) = 0.8.

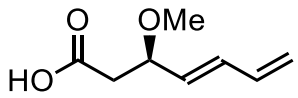
$[\alpha]_{25}^{D}$= +118 (*c* = 1.50, $CHCl_3$, 85% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79–7.77 (m, 2H), 7.42–7.32 (m, 2H) 6.30–6.23 (m, 2H), 5.43 (dd, *J* = 14.0 Hz, 7.6 Hz, 1H), 5.29–5.22 (m, 1H), 5.17–5.14 (m, 1H), 4.01–-3.95 (m, 2H), 3.88–3.79 (m, 1H), 3.25 (s, 3H), 2.44 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 135.9, 135.6, 133.1, 130.0 (2), 128.4, 128.1 (2), 119.2, 79.3, 71.6, 56.9, 21.8 ppm.

FTIR (Neat): λ^{-1} = 1359, 1189, 1175 cm^{-1}.

HRMS (CI): Calcd. for $C_{14}H_{19}O_4S$ ($M+H^+$): 283.1001, found 283.1004.



(*R*,*E*)-3-Methoxyhepta-4,6-dienoic acid (1.64)

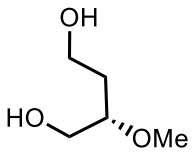
To a solution of (*S*,*E*)-2-methoxyhexa-3,5-dienyl 4-methylbenzenesulfonate (340 mg, 1.38 mmol), [18]-crown-6 (360 mg, 1.40 mmol), tetrabutylammonium iodide (100 mg, 0.28 mmol) in dimethyl sulfoxide (1.3 mL) was added potassium cyanide (270 mg, 4.14 mmol) and stirred at 45 °C for 2 h. The crude reaction mixture was added to ether (10 mL) and then water (30 mL) was added. The resulting mixture was extracted with ether (3 x 30 mL). The organic extracts were combined and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure and diluted with ethanol (6 mL). Then 30% hydrogen peroxide (6 mL) and lithium hydroxide hydrate (283 mg, 11.9 mmol) were added at ambient temperature. The resulting solution was stirred for 24 h. Brine (10 mL) was added and the reaction mixture was washed with ether (2 x 20 mL) and the aqueous layer was neutralized with citric acid (2.5 g, 12 mmol). The resulting mixture was extracted with ether (3 x 30 mL), the combined organic extracts were washed with brine (10 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give acid **1.64** (135 mg, 0.12 mmol, 72% yield). To corroborate the assignment of absolute stereochemistry, the optical rotation was compared to a known compound.[32]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.38–6.24 (m, 2H), 5.55 (dd, *J* = 14.5 Hz, 8.0 Hz, 1H), 5.26 (dd, *J* = 15.9 Hz, 1.9 Hz, 1H) 5.15 (dd, *J* = 9.7 Hz, 1.9 Hz, 1H), 4.10–4.05 (m, 1H), 3.30 (s, 3H), 2.68–2.51 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 136.0, 134.4, 131.8, 118.9, 78.3, 56.7, 41.0 ppm

$[\alpha]_{26}^{D}$= +6.5 (*c* = 0.61, $CHCl_3$, 85% *ee*)

Lit. $[\alpha]_{26}^{D}$= +7.8 (*c* = 0.61, $CHCl_3$, 98% *ee*)[32]

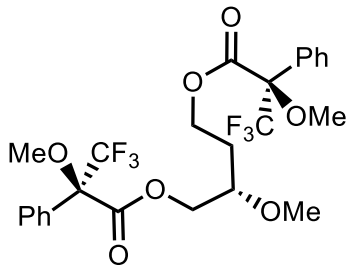


(*S*)-2-methoxybutane-1,4-diol (1.9R)

Acid **1.64R** (40 mg, 0.25 mmol), methanol (5 mL), and benzene (15 mL) were combined under an atmosphere of nitrogen, cooled to 0 °C. 4 tms was added, and the cooling bath was removed. After 1 h at ambient temperature the reaction mixture was concentrated under reduced pressure. Dichloromethane (20 mL) was added and reaction vessel was cooled to -78 °C. Ozone was bubbled into the solution until a blue color persisted. The cooling bath was removed and stream of nitrogen was used to concentrate the mixture to dryness. The resulting residue was dissolved in tetrahydrofuran (10 mL) under an atmosphere of nitrogen and cooled with an ice bath. Lithium aluminum hydride (2.5 mL, 2.5 mmol, 1 M in tetrahydrofuran) was added, the cooling bath was removed and the resulting mixture was stirred at ambient temperature for 16 h. The reaction vessel was cooled with an ice bath, water (0.1 mL) was added, followed by NaOH (0.3 mL, 15% solution) and water (0.4 mL), the resulting mixture was stirred vigorously. Magnesium sulfate (5 g) was added to the reaction mixture, filtered, concentrated under reduced pressure and resulting residue was purified via column chromatography (SiO_2, hexanes/ethyl acetate, 30%-100% gradient elution) to furnish diol **1.9R** (20 mg, 0.17 mmol, 65% yield). The data collected for the compound was consistent with the known values:[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (m, 3H), 3.58 (dd, *J* = 4.5, 11.4 H, 1H), 3.48 (m, 1H), 3.42 (s, 3H), 2.4 (br s, 2H), 1.86-1.81 (m, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 80.1, 63.3, 59.7, 57.1, 33.4 ppm

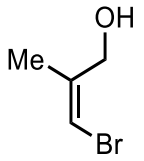


(2*R*,2'*R*)-(*S*)-2-methoxybutane-1,4-diyl bis(3,3,3-trifluoro-2-methoxy-2-phenylpropanoate) (3.25)

The following procedure is a modification of the prior report[127], which allowed the title compound to prepared in higher yield Diol **1.9R** (20 mg, 0.17 mmol), dichloromethane (5 mL), (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) (312 mg, 1.33 mmol), 4-dimethylamino pyridine (2 mg, 0.02 mmol) were combined under an atmosphere of nitrogen. The reaction vessel was cooled with an ice batch, DCC (275 mg, 1.33 mmol) was added and the cooling bath was removed. Dichloromethane (10 mL) was added, the resulting mixture was filtered, concentrated under reduced pressure and resulting residue was purified via column chromatography (SiO_2, hexanes/ethyl acetate, 10%-30% gradient elution) to furnish bis(Mosher ester) **3.25** (20 mg, 0.17 mmol, 65% yield). The data collected for the compound was consistent with the known values:[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.5 (m, 4H), 7.39 (m, 6H), 4.32-4.49 (m, 3H), 4.13 (dd, *J* = 11.5, 5.6 Hz, 1H), 3.54 (s, 3H), 3.53 (s, 3H), 3.40 (m, 1H), 3.29 (s, 3H), 1.70-1.88 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 166.3, 132.1, 132.0, 129.5, 128.4, 128.3, 127.2, 127.2, 124.4, 124.3, 122.1, 122.0, 84.8, 84.6, 84.5, 84.4, 75.0, 65.9, 62.3, 55.8, 55.3, 30.6 ppm



(*Z*)-3-Bromo-2-methylprop-2-ene-1-ol (3.15)

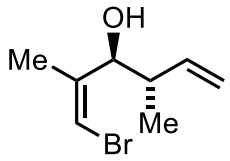
The following procedure is a modification of the prior report, which allowed the title compound to prepared in higher yield. A solution of MeMgBr (52 mL, 160 mmol, 220 mol %, 3 M in Et_2O) was added dropwise to a stirred suspension of freshly distilled propargylalcohol (4.00 g, 71.4 mmol, 100 mol %) and CuI (1.36 g, 7.14 mmol, 10 mol %) in THF (70 mL, 1 M) at –10°C. After addition the cooling bath was removed and the dark suspension was stirred for a further 16 h at 25 °C. The suspension was cooled to –78 °C and trimethylborate (9.7 mL, 8.9 g, 86 mmol, 120 mol %) was added. The reaction mixture was stirred for an additional 30 min at 25 °C after the cooling bath was removed. The reaction mixture was transferred to a separatory funnel containing HCl (aq.) (100 mL, 2 M). The organic layer was washed and separated and the aqueous layer was

extracted with Et_2O (3 x 50 mL). The combined organic extracts were concentrated under reduced pressure to roughly half their initial volume. The organic layer was transferred to a separatory funnel and was extracted with NaOH (aq.) (4 x 25 mL, 8 M). The combined aqueous layers were washed with Et_2O (2 x 25 mL), then acidified with aq. HCl (approx. 140 mL, 6 M) so that color change (from yellow to colorless) occurred. The acidic aqueous layer was then extracted with Et_2O (6 x 40 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue (4.1 g) was dissolved in MeOH (82 mL, 0.5 M) and a solution of $CuBr_2$ (28.1 g, 126 mmol, 300 mol %) in water (82 mL) was added. The dark solution was stirred under reflux for 22 h. Brine (80 mL) was added at 25 °C and the aqueous layer was extracted with Et_2O (6 x 80 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 10–50% DCM/hexanes) to furnish the title compound **3.15** as a light yellow oil (3.74 g, 24.8 mmol) in 21% yield.

.**R_f** = 0.34 (SiO_2, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.98 (s, 1H), 4.29 (s, 2H), 1.97 (s, 1H), 1.89 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 101.9, 63.6, 20.1 ppm.



(*Z*,*3S*,*4S*)-1-Bromo-2,4-dimethyl-3-hydroxyhexa-1,5-diene (3.14)

(*S*)-Ir-complex (103 mg, 0.099 mmol, 5 mol %), vinylbromide **3.15** (300 mg, 1.99 mmol, 100 mol %), and Na_2CO_3 (105 mg, 0.994 mmol, 50 mol %) were suspended in THF (1.0 mL, 2 M) at 25 °C in a resealable pressure tube (13 x 100 mm). α-Methyl allyl acetate (454 mg, 3.97 mmol, 200 mol %) and degassed water (180 mg, 9.94 mmol, 500 mol %) were added and the mixture was stirred under an atmosphere of argon at 70 °C for 6 d. The reaction mixture was concentrated under reduced pressure and the residue was chromatographically purified (SiO_2, 5–10% EtOAc /hexanes) to furnish the title compound **3.14** (267 mg, 1.30 mmol, dr = 12:1, *anti*:*syn*, 94% ee) in 66% yield as pale yellow oil. The stereochemical assignment was inferred based on analogy with the literature precedent.[79]

R_f = 0.38 (SiO_2, hexanes/EtOAc = 5 : 1).

$[\alpha]_{26}^{D}$= +178 (c = 0.37, $CHCl_3$ 96% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.07 (qd, *J* = 1.5 Hz, 0.5 Hz, 1H), 5.80 (ddd, *J* = 17.1 Hz, 10.3 Hz, 8.6 Hz, 1H), 5.20 (ddd, *J* = 17.1 Hz, 1.8 Hz, 0.9 Hz, 1H), 5.19 (ddd, *J* = 10.3 Hz, 1.8 Hz, 0.5 Hz, 1H), 4.49 (d, *J* = 9.0 Hz, 1H), 2.40–2.31 (m, 1H), 1.79 (d, *J* = 1.5 Hz, 3H), 1.55 (s, 1H), 0.97 (d, *J* = 6.9 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 140.6, 117.1, 103.4, 74.1, 42.8, 17.2, 15.9 ppm.

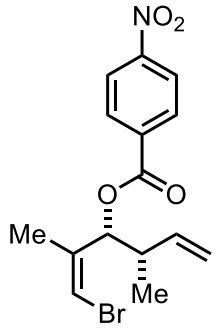
FTIR (ATR): 3423 (m), 3077 (w), 2970 (m), 2920 (m), 2161 (w), 1637 (m), 1436 (m), 1375 (m), 1292 (m), 1008 (vs), 915 (s), 725 (s) cm^{-1}.

HRMS (CI): Calcd. for $C_8H_{14}OBr$ (MH): 205.0228; Found: 205.0225.

GC: (Cyclosil-B: Initial temperature: 50 °C (3 min hold), final temperature: 200 °C; rate: 10 K/min): (*Z*)-*anti*-diastereoisomer: t_{major} = 13.4 min, t_{minor} = 13.5 min

(*Z*)-*syn*-diastereoisomer: t_{major} = 13.6 min; (*E*)-diastereoisomer: t = 14.1 min

ee = 94%, *dr* = 12:1



(3*R*,4*S*,*Z*)-1-Bromo-2,4-dimethylhexa-1,5-dien-3-yl 4-nitrobenzoate (3.29)

Diisopropyl azodicarboxylate (0.23 mL, 1.2 mmol, 220 mol %) was added dropwise to a solution of compound **3.14** (110 mg, 0.54 mmol, 100 mol %), PPh_3 (281 mg, 1.07 mmol, 200 mol %), ethyldiisopropylamine (0.18 mL, 1.1 mmol, 200 mol %) and 4-nitrobenzoic acid (179 mg, 1.07 mmol, 200 mol %) in THF (35 mL, 0.015 M) at 0 ºC under an atmosphere of argon. The reaction mixture was stirred at 0 ºC for 3 h. The crude reaction mixture was concentrated under reduced pressure and the residue was purified chromatographically (SiO_2, 10% EtOAc/hexanes) to furnish **3.29** (150 mg, 0.42 mmol) in 79% yield as a colorless solid.

R_f = 0.43 (SiO_2, hexanes/EtOAc = 5 : 1).

MP: 49–50 °C (rac), 62–63 °C.

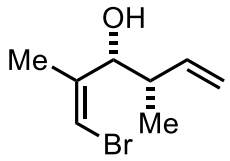
$[\alpha]_{26}^{D}$= +139 (c = 1.03, $CHCl_3$ 96% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33–8.29 (m, 2H), 8.25–8.22 (m, 2H), 6.16–6.13 (m, 1H), 5.89 (d, *J* = 8.8 Hz, 1H), 5.78 (ddd, *J* = 17.1 Hz, 10.3 Hz, 8.1 Hz, 1H), 5.14 (dt, *J* = 17.1 Hz, 1.2 Hz, 1H), 5.08 (ddd, *J* = 10.3 Hz, 1.5 Hz, 0.5 Hz, 1H), 2.88–2.79 (m, 1H), 1.80 (d, *J* = 1.5 Hz, 3H), 1.19 (d, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 150.6, 137.8, 137.4, 135.4, 130.7, 123.7, 116.1, 105.4, 78.6, 40.5, 18.4, 16.5 ppm.

FTIR (ATR): 3111 (w), 3080 (w), 2975 (m), 2922 (m), 2854 (w), 1727 (s), 1527 (s), 1319 (m), 1270 (vs), 1101 (s), 952 (m), 719 (s) cm^{-1}.

HRMS (CI): Calcd. for $C_{15}H_{17}NO_4Br$ (MH^+): 354.0341; Found: 354.0343.



(*Z*,*3R*,*4S*)-1-Bromo-2,4-dimethyl-3-hydroxyhexa-1,5-diene (3.30)

Ester **3.29** (3.77 g, 10.6 mmol, 100 mol %) was dissolved in a mixture of THF, MeOH and water (71 mL, 0.15 M, 5:1:1 volume ratios, respectively) at 25 °C. Then $LiOH•H_2O$ (3.57 g, 85.1 mmol, 800 mol %) was added and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was transferred to a separatory funnel and the organic layer was washed with brine (70 mL). The aqueous layer was extracted with diethyl ether (3 x 70 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 10–20% EtOAc/hexanes) to furnish the title compound **3.30** (2.15 g, 10.5 mmol) in 99% yield as a light yellow oil.

R_f = 0.38 (SiO_2, hexanes/EtOAc = 5 : 1).

$[\alpha]_{28}^{D}$= +30.9 (c = 1.25 , $CHCl_3$ 96% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97–5.95 (m, 1H), 5.71 (ddd, *J* = 17.2 Hz, 10.3 Hz, 7.9 Hz, 1H), 5.06 (ddd, *J* = 17.2 Hz, 1.7 Hz, 1.2 Hz, 1H), 5.01 (ddd, *J* = 10.4 Hz, 1.8 Hz, 0.9 Hz, 1H), 4.56 (d, *J* = 8.4 Hz, 1H), 2.52–2.42 (m, 1H), 1.85 (s, 1H), 1.79 (d, *J* = 1.5 Hz, 3H), 1.16 (d, *J* = 6.7 Hz, 3H) ppm.

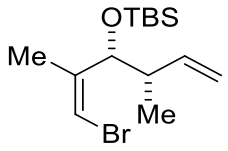
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 139.4, 115.1, 102.4, 74.9, 41.9, 17.7, 16.2 ppm.

FTIR (ATR): 3371 (m), 3076 (w), 2975 (m), 2922 (m), 1641 (m), 1436 (m), 1374 (m), 1292 (m), 1008 (vs), 915 (s), 716 (s) cm^{-1}.

GC: (Cyclosil-B: Initial temperature: 50 °C (3 min hold), final temperature: 200 °C; rate: 10 K/min): (*Z*)-*anti*-diastereoisomer: t_{major} = 13.5 min,

(*Z*)-*syn*-diastereoisomer: t_{major} = 13.8 min; t_{minor} = 13.7 min

ee = 93%, *dr* = 17 : 1



(3*R*,4*S*,*Z*)-1-Bromo-2,4-dimethylhexa-1,5-dien-3-yloxy)(*tert*-butyl)dimethylsilane (3.12)

To a stirred solution of compound **3.30** (40 mg, 0.195 mmol) and 2,6-lutidine (48 μL, 0.39 mmol) in dichloromethane (2 mL) at 0 ^{o}C under an atmosphere of argon was added TBS-OTf (31.5 μL, 0.195 mmol). After 1 h the crude mixture was concentrated under reduced pressure and purified (SiO_2, 10% ether/hexanes) to give **3.12** (58 mg, 95% yield).

R_f (SiO_2, hexanes : ethyl acetate = 9 : 1) = 0.9.

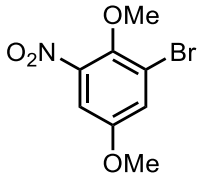
$[\alpha]_{28}^{D}$= +30.9 (c = 1.25 , $CHCl_3$ 96% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87 (qd, *J* = 1.5 Hz, *J* = 0.4 Hz, 1H), 5.68 (ddd, *J* = 17.2 Hz, *J* = 10.3 Hz, *J* = 8.2 Hz, 1H), 4.99 (ddd, *J* = 17.2 Hz, *J* = 1.9 Hz, *J* = 1.1 Hz, 1H), 4.93 (ddd, *J* = 10.3 Hz, *J* = 1.9 Hz, *J* = 0.7 Hz, 1H), 4.45 (d, *J* = 8.8 Hz, 1H), 2.31−2.40 (m, 1H), 1.73 (d, 1.5 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.65, 139.73, 114.29, 101.43, 75.67, 43.18, 25.79, 18.11, 17.41, 17.00, −4.82, −5.00.

IR (neat): λ^{-1} = 3078, 2956, 2929, 2857, 1641, 1462, 1252, 1067, 913, 837.

HRMS calcd. for $C_{14}H_{28}BrOSi$ (M+H): 319.1093; Found: 319.1104



Bromo-2,5-dimethoxy-3-nitrobenzene

Dimethylsulfate (3.05 g, 34.2 mmol, 200 mol %) was added at 25 °C to a stirred suspension of K_2CO_3 (5.02 g, 36.3 mmol, 300 mol %) and bromomethoxynitrophenol (3.00 g, 12.1 mmol, 100 mol %) in acetone (60 mL, 0.2 M). After stirring the mixture at reflux for 16 h, the solvent was removed under reduced pressure. Flash column chromatography (SiO_2, 10–20% EtOAc/hexanes) furnished the title compound 1-bromo-2,5-dimethoxy-3-nitrobenzene as a yellow solid (3.02 g, 11.5 mmol, 95% yield).

R_f = 0.45 (SiO_2, hexanes/EtOAc = 5 : 1).

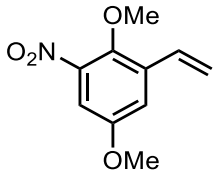
MP: 100-101°C. (Lit.: 98–98.5 °C)[129]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 3.1 Hz, 1H), 7.28 (d, *J* = 3.1 Hz, 1H), 3.96 (s, 3H), 3.83 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 145.0, 144.4, 123.8, 120.1, 109.2, 62.7, 56.2 ppm.

FTIR (ATR): 3102 (w), 2946 (w), 2840 (w), 1524 (s), 1475 (m), 1341 (m), 1229 (m), 1042 (m) cm^{-1}.

HRMS (CI): Calcd. for $C_8H_8NO_4Br$ (M): 260.9637; Found: 260.9635.



2,5-Dimethoxy-1-nitro-3-vinylbenzene (3.16)

1-Bromo-2,5-dimethoxy-3-nitrobenzene (131 mg, 0.500 mmol, 100 mol %), triphenylphosphine (10.5 mg, 0.040 mmol, 8 mol %), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol, 2 mol %), Cs_2CO_3 (489 mg, 1.50 mmol, 300 mol %), and potassium vinyltrifluoroborate (67 mg, 0.50 mmol, 100 mol %) were added to a resealable pressure tube (13 x 100 mm). THF (2.1 mL, 2 M) and H_2O (0.2 mL) were added in oxygen free conditions and the mixture was stirred under argon at 85 °C for 2 d. Saturated NH_4Cl solution (2 mL) was added, the layers were separated and the aqueous layer was extracted with DCM (3 x 2 mL). The combined organic phases were dried ($MgSO_4$), the mixture filtered and the solvent removed under reduced pressure. Flash column chromatography (SiO_2, 10–20% EtOAc/hexanes) furnished 2,5-dimethoxy-1-nitro-3-vinylbenzene **3.16** (96 mg, 0.46 mmol, 92% yield) as a yellow solid.

R_f = 0.39 (SiO_2, hexanes/EtOAc = 5 : 1).

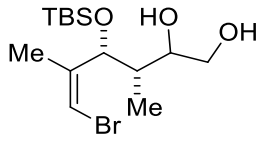
MP: 54–55 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 3.2 Hz, 1H), 7.24 (d, *J* = 3.2 Hz, 1H), 6.97 (dd, *J* = 17.7 Hz, 11.1 Hz, 1H), 5.82 (dd, *J* = 17.7 Hz, 0.9 Hz, 1H), 5.47 (dd, *J* = 11.1 Hz, 1.1 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 144.6, 144.6, 134.9, 129.9, 117.8, 116.9, 108.6, 63.1, 56.0 ppm.

FTIR (ATR): 3090 (w), 2941 (w), 2837 (w), 1528 (s), 1477 (m), 1414 (m), 1352 (m), 1230 (m), 1071 (w), 994 (s) cm^{-1}.

HRMS (CI): Calcd. for $C_{10}H_{11}NO_4$ (M): 209.0688; Found: 209.0692.



(3*S*,4*R*,*Z*)-6-Bromo-4-(*tert*-butyldimethylsilyloxy)-3,5-dimethylhex-5-ene-1,2-diol (3.31diol)

To a solution of **3.12** (80 mg, 0.25 mmol), *N*-methylmorpholine-*N*-oxide (58 mg, 0.50 mmol), and water (0.01 ml), 0.5 mmol) in dichloromethane (2 mL) was added osmium tetraoxide (3.4 mg, 0.012 mmol). The resulting mixture was stirred at ambient temperature for 2 h until the complete conversion of starting material was observed by TLC. $NaHSO_3$ (200 mg) was added and the reaction mixture was decanted. The crude reaction mixture was concentrated and purified (SiO_2, 50% ethyl acetate/hexanes) to give **3.31diol** (80 mg, 90% yield) as white solid.

R_f (SiO_2, hexanes : ethyl acetate = 1 : 1) = 0.46.

mp = 68−69°C (rac), 77−78°C (93% ee).

$[\alpha]_{25}^{D}$= −24 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): (major diastereomer, *dr* = 5 : 1) δ = 6.00 (s, 1H), 4.88 (d, *J* = 5.3 Hz, 1H), 3.60−3.68 (m, 1H), 3.52 (dd, *J* = 11.0 Hz, *J* = 6.5 Hz, 1H), 2.30 (s, br, 2

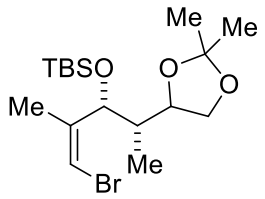
OH), 2.00−2.09 (m, 1H), 1.88 (s, 3H), 0.91 (s, 9H), 0.90 (d, J = 7.2 Hz, 3H), 0.14 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.31, 102.35, 74.46, 73.76, 64.68, 41.01, 25.73, 18.88, 17.99, 11.64, −4.87, −5.00.

IR (neat): λ^{-1} 3383, 2955, 2928, 2857, 1462, 1252, 1041, 870, 837.

HRMS calcd. for $C_{14}H_{30}BrOSi$ (M+H): 353.1148; Found: 353.1149.

$[\alpha]_{25}^{D}$= −34.0 (c = 1.00, $CHCl_3$).



((3*R*,4*S*,*Z*)-1-Bromo-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpent-1-en-3-yloxy)(*tert*-butyl)dimethylsilane (3.31)

To a solution of **3.31diol** (565 mg, 1.60 mmol) and 2,2-dimethoxypropane (5.7 mL, 16.0 mmol) in dichloromethane (10 mL) under an atmosphere of argon was added pyridinium *p*-toluenesulfonate (40 mg, 0.16 mmol) at ambient temperature. The mixture was stirred for 1 h, concentrated onto silica gel under reduced pressure, and purified (SiO_2, 10% ether/hexanes) to give **3.31** (590 mg, 94% yield) as clear oil. :

R_f (SiO_2, hexanes : ethyl acetate = 5 : 1) = 0.54.

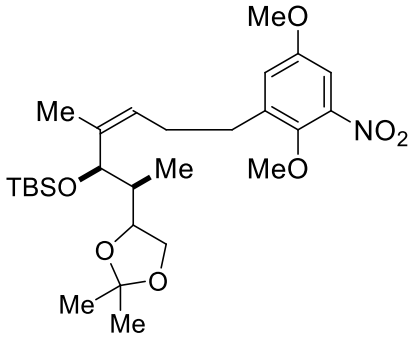
$[\alpha]_{25}^{D}$= −14.4 (c = 1.08, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): major diastereomer, *dr* = 5 : 1 (NMR) δ =5.90 (qd, *J* = 1.5 Hz, *J* = 1.0 Hz, 1H), 4.70 (dd, *J* = 5.6 Hz, *J* = 0.8 Hz, 1H), 4.00 (dd, *J* = 7.9 Hz, *J* = 6.3 Hz, 1H), 3.92 (td, *J* = 7.2 Hz, *J* = 6.3 Hz, 1H), 3.64 (dd, *J* = 7.8 Hz, *J* = 7.5 Hz, 1H), 1.97 (qdd, *J* = 6.9 Hz, *J* = 6.8 Hz, *J* = 5.7 Hz, 1H), 1.79 (d, *J* = 1.5 Hz, 3H), 1.41 (d, *J* = 0.5 Hz, 3H), 1.33 (d, *J* = 0.5 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.72, 108.40, 100.51, 76.17, 72.77, 67.17, 41.30, 26.54, 25.84, 25.42, 18.80, 18.13, 10.02, −4.90, −5.15.

IR (neat): λ^{-1} 2983, 2955, 2929, 2857, 1472, 1369, 1252, 1213, 1161, 1121, 1047, 859, 839, 775.

HRMS calcd. for $C_{17}H_{32}BrO_3Si$ (M-H): 391.1304; Found: 391.1304.



***tert*-Butyl[(2*S*,3*R*,*Z*)-7-(2,5-dimethoxy-3-nitrophenyl)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-methylhept-4-en-3-yloxy]dimethylsilane (3.32)**

To a solution of **3.31** (400 mg, 1.02 mol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (41 mg, 0.05 mmol), cesium carbonate (0.98 g, 2.85 mmol), and water (0.4 ml) in dimethyl acetamide (6 mL)

under an atmosphere of argon was added a solution of **3.16** (3 ml, 1.52 mmol, 0.5 M in tetrahydrofuran). The resulting black solution was stirred at 50 ^{o}C for 48 h. The reaction mixture was added to brine (60 mL) and extracted with ether (3 x 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered, concentrated under reduced pressure and purified purified (SiO_2, 50% to 100% dichloromethane/hexanes, gradient elution) to give **3.32** (291 mg, 55% yield) as yellow oil

R_f (SiO_2, hexanes : ethyl acetate = 5 : 1) = 0.26.

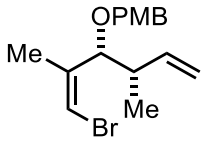
$[\alpha]_{25}^{D}$ = −18.2 (*c* = 0.45, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 3.2 Hz, 1H), 6.99 (d, *J* = 3.2 Hz, 1H), 5.18 (ddt, *J* = 8.0 Hz, *J* = 6.5 Hz, *J* = 1.3 Hz, 1H), 4.70 (d, *J* = 2.6 Hz, 1H), 3.85 (s, 3H), 3.82–3.98 (m, 2H), 3.81 (s, 3H), 3.51 (t, *J* = 7.3 Hz, 1H), 2.70 (t, *J* = 7.8 Hz, 2H), 2.40–2.50 (m, 1H), 2.17–2.27 (m, 1H), 1.72 (d, *J* = 0.9 Hz, 3H), 1.57–1.67 (m, 1H), 1.33 (s, 6H), 0.90 (s, 9H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.04 (s, 3H), −0.06 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ =154.96, 145.57, 144.06, 139.67, 139.40, 124.02, 121.65, 108.49, 106.66, 76.68, 70.28, 67.96, 62.71, 55.81, 44.16, 29.90, 28.11, 26.64, 25.87, 25.61, 20.22, 18.20, 9.76, −4.95, −5.25.

IR (neat): λ^{-1} 2954, 2930, 2856, 1619, 1536, 1473, 1426, 1368, 1234, 1181, 1053, 1004, 838, 774.

HRMS calcd. for $C_{27}H_{46}NO_7Si$ (M+H): 524.3044; Found: 524.3035.



(*Z*,*3R*,*4S*)-1-Bromo-3-(4-methoxybenzyloxy)-2,4-dimethylhexa-1,5-diene (3.37)

NaH (807 mg, 20.2 mmol, 60% in mineral oil, 300 mol %) was added portion wise to a solution of alcohol **3.30** (1.38 g, 6.73 mmol, 100 mol %) at 0 °C. *p*-Methoxybenzyl chloride (1.58 g, 10.1 mmol, 150 mol %) was added as a solution in THF–DMSO (34 mL, 0.2 M, 5:1, volume ratio, respectively). The cooling bath was removed and the reaction mixture was allowed to stir 2 h. A saturated solution of $NaHCO_3$ (aq) (30 mL) was carefully added and the reaction mixture transferred to a separatory funnel. The aqueous layer was extracted with diethyl ether (3 x 30 mL), the combined organic extracts were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, 0–5% EtOAc/hexanes) to furnish the title compound **3.37** (1.75 g, 5.38 mmol) in 80% yield as a light yellow oil.

R_f = 0.57 (SiO_2, hexanes/EtOAc = 5 : 1).

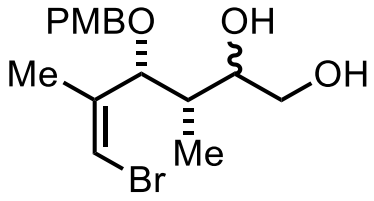
$[\alpha]_{26}^{D}$= +32 (c = 1.3, $CHCl_3$ 94% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.24 (m, 2H), 6.89–6.85 (m, 2H), 6.13 (qd, *J* = 1.4 Hz, 0.5 Hz, 1H), 5.63 (dddd, *J* = 17.2 Hz, 10.2 Hz, 8.4 Hz, 0.5 Hz, 1H), 5.03–4.98 (m, 1H), 4.93 (ddt, *J* = 10.3 Hz, 1.8 Hz, 0.8 Hz, 1H), 4.41 (d, *J* = 11.3 Hz, 1H), 4.22 (d, *J* = 9.4 Hz, 1H), 4.21 (d, *J* = 11.3 Hz, 1H), 3.83 (s, 3H), 2.43 (tq, *J* = 8.5 Hz, 6.6 Hz, 1H), 1.75 (dd, *J* = 1.5 Hz, 0.6 Hz, 3H), 1.13 (d, *J* = 6.6 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 139.9, 139.3, 130.4, 129.6, 114.6, 113.6, 104.7, 81.5, 70.3, 55.2, 41.2, 17.4, 17.4 ppm.

FTIR (ATR): 3072 (w), 2959 (m), 2929 (m), 2835 (w), 1641 (m), 1513 (s), 1246 (vs), 1172 (m), 1109 (s), 1064 (s) cm^{-1}.

HRMS (CI): Calcd. for $C_{16}H_{20}BrO_2$ ($M-H^+$): 323.0647; Found: 323.0651.



(*3S*,*4R*,*5Z*)-6-Bromo-4-(4-methoxybenzyloxy)-3,5-dimethylhex-5-ene-1,2-diol (3.38)

NMO (144 mg, 1.23 mmol, 200 mol %) was added to a solution of olefin **3.37** (200 mg, 0.615 mmol, 100 mol %) and osmium tetroxide (3 mg, 0.01 mmol, 2 mol %) in DCM (6.0 mL, 0.1 M) at 25 °C. Water (22 mg, 1.2 mmol, 200 mol %) was added and the solution was allowed to stir for 4 h at 25 °C. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2, 30–50% EtOAc/hexanes) to furnish the title compound **3.38** (214 mg, 0.595 mmol) in 97% yield as a highly viscous colorless oil.

R_f = 0.24 (SiO_2, hexanes/EtOAc = 1 : 1).

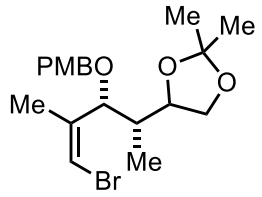
$[\alpha]_{25}^{D}$= +26 (c = 0.80, 94% *ee* $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): major diastereoisomer, *dr* = 4:1 (NMR) δ 7.28–7.25 (m, 2H), 6.92–6.87 (m, 2H), 6.19 (s, br, 1H), 4.60 (d, *J* = 5.3 Hz, 1H), 4.45 (d, *J* = 11.4 Hz, 1H), 4.19 (d, *J* = 11.3 Hz, 1H), 3.81 (s, 3H), 3.68–3.60 (m, 2H), 3.52–3.46 (m, 1H), 2.89 (s, br, 2H), 2.11–2.03 (m, 1H), 1.90–1.88 (m, 3H), 0.99 (d, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 140.7, 129.7, 129.5, 113.9, 104.4, 79.2, 74.3, 70.8, 64.7, 55.2, 39.2, 18.9, 11.7 ppm.

FTIR (ATR): 3404 (m), 3069 (w), 2922 (m), 2882 (m), 2836 (w), 1612 (m), 1513 (m), 1246 (s), 1033 (s) cm^{-1}.

HRMS (CI): Calcd. for $C_{16}H_{22}BrO_4$ ($M-H^+$): 357.0701; Found: 357.0699.



4-[(*2R*,*3R*,*4Z*)-5-Bromo-3-(4-methoxybenzyloxy)-4-methylpent-4-en-2-yl]-2,2-dimethyl-1,3-dioxolane (3.39)

2,2-Dimethoxypropane (812 mg, 7.79 mmol, 1000 mol %) was added to a solution of diol **3.38** (280 mg, 0.779 mmol, 100 mol %) in DCM (8.0 mL, 0.1 M) at 25 °C. Then *p*-Toluenesulfonic acid (10 mg, 0.04 mmol, 5 mol %) was added and the solution was stirred at 25 °C under nitrogen for 17 h. After completion of the reaction the solvent was removed under reduced pressure and the residue was purified by column chromatography

(SiO_2, 10–20% EtOAc/hexanes) to furnish the title compound **3.39** (308 mg, 0.771 mmol, 99% yield) as a viscous colorless oil.

R_f = 0.54 (SiO_2, hexanes/EtOAc = 5 : 1).

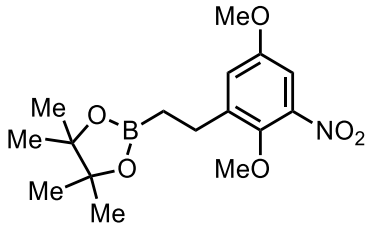
$[\alpha]_{26}^{D}$ = −1.4 (c = 1.38, $CHCl_3$ 94% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): major diastereoisomer, *dr* = 3 : 1 (NMR) δ 7.27–7.25 (m, 2H), 6.89–6.86 (m, 2H), 6.13 (qd, *J* = 1.4 Hz, 0.7 Hz, 1H), 4.39 (d, *J* = 11.2 Hz, 1H), 4.31 (dd, *J* = 7.2 Hz, 0.7 Hz, 1H), 4.22 (d, *J* = 11.3 Hz, 1H), 4.01–3.91 (m, 2H), 3.80 (s, 3H), 3.69–3.60 (m, 1H), 2.14 (dqd, *J* = 7.2 Hz, 6.8 Hz, 5.8 Hz, 1H), 1.82 (d, *J* = 1.5 Hz, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 0.96 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 140.9, 130.3, 129.5, 113.6, 108.2, 103.9, 79.5, 76.3, 70.6, 66.3, 55.2, 38.8, 26.4, 25.3, 18.4, 10.2 ppm.

FTIR (ATR): 3064 (w), 2982 (m), 2934 (m), 2857 (w), 1612 (m), 1513 (s), 1369 (m), 1246 (s), 1036 (vs) cm^{-1}.

HRMS (CI): Calcd. for $C_{19}H_{26}BrO_4$ ($M-H^+$): 397.1014; Found: 397.1018.



2-(2,5-dimethoxy-3-nitrophenethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.40)

To a stirred solution of $[Ir(cod)Cl]_2$ (88 mg, 0.13 mmol, 2.5 mol %), 1,2-bis(diphenylphosphino)ethane (171 mg, 0.274 mmol, 5.2 mol %), toluene (4.5 mL), 1,2-

dichloroethane (0.5 mL) under argon at 25 °C was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.89 mL, 13 mmol, 250 mol %) followed by 2,5-dimethoxy-1-nitro-3-vinylbenzene (1.1 g, 5.2 mmol, 100 mol %). The resulting solution was stirred for 14 h. The reaction mixture was added to ether (50 mL) and methanol (3 mL) was added slowly. After gas evolution ceased, brine (10 mL) was added and the organic layer was washed, dried (Na_2SO_4), filtered, concentrated, and purified via column chromatography (SiO_2, 20-100% dichloromethane/hexanes, gradient elution) to give 1.5 g the title compound **3.40** (1.56 g, 4.63 mmol, 88 % yield) as a yellow solid.

R_f = 0.2 (SiO_2, hexanes/DCM = 1 : 1).

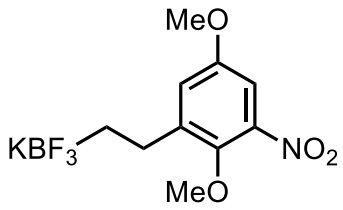
MP: 36–37 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 3.2 Hz, 1H), 7.04 (d, *J* = 3.2 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 2.78 (t, *J* = 8.1 Hz, 2H), 1.22 (s, 12H), 1.12 (t, *J* = 8.1 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$, C attached to quadropole B not observed): δ 156.8, 147.1, 145.8, 143.6, 122.6, 108.5, 85.1, 64.5, 57.7, 26.6, 25.8 ppm.

FTIR (ATR): λ^{-1} 2977, 1530, 1369, 1319, 1229, 1141, 1050 cm^{-1}.

HRMS (ESI): Calcd. for $C_{16}H_{24}NBO_6$ ($M+Na^+$): 360.1594, found 360.1592.



Potassium trifluoroborate salt (3.41)

A mixture of $[Ir(cod)Cl]_2$ (192 mg, 0.287 mmol), 1,2-bis(diphenylphosphino)ethane (358 mg, 0.574 mmol), toluene (5 mL), and dichloroethane was sparged with argon. 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (2.4 mL, 36 mmol) was added to the mixture followed by nitro styrene **3.16** (2.5 g, 11.9 mmol) dissolved in toluene (18 mL). The resulting mixture was stirred for 2 h, and added a solution of diethyl ether (50 mL), methanol (5 mL) and water (5 mL). After gas evolution ceased, brine (10 mL) was added and the organic layer was washed, dried (Na_2SO_4), filtered, concentrated, and purified via column chromatography (SiO_2, 50-100% dichloromethane/hexanes, gradient elution) to give 3.5 g of the intermediate pinacol ester as a yellow oil. The residue was diluted with tetrahydrofuran (10 mL) and cooled to 0 °C. Potassium hydrogen fluoride was added followed by water (2 mL), the resulting mixture was stirred overnight at ambient temperature. The reaction mixture was concentrated to dryness under reduced pressure, to give an off white solid, which was suspended in hot acetone and filtered. The filtrate was concentrated in the minimal amount of hot acetone, added to a solution of diethyl ether and filtered to provide the title compound **(3.41)** as a yellow powder (2.81 g, 10.0 mmol, 84% yield)

MP: 189-190 °C.

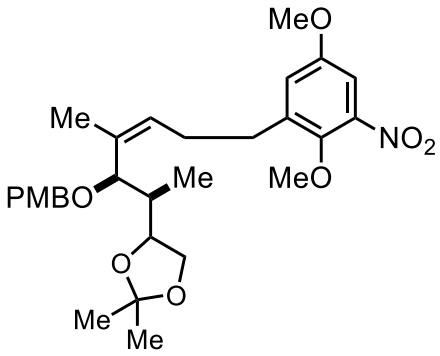
^{1}H NMR (400 MHz; acetone): δ 7.09 (d, *J* = 3.2, 1H), 7.06 (d, *J* = 3.2, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 2.67-2.62 (m, 2H), 0.57-0.48 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$, C attached to quadropole B not observed): δ 156.2, 146.4, 145.7, 145.2, 121.1 106.3, 63.1, 53.3, 26.2 ppm.

^{19}F NMR -141.8 ppm.

FTIR (ATR):): λ^{-1} 3555, 1525, 1340, 1318, 1267, 1223, 1074, 1050, 1024 cm^{-1}.

MS (ESI): Calcd. for $C_{10}H_{12}BF_3KNO_4$ ($M\text{-}K^+$): 278, found 278.



4-[(*2R*,*3R*,*4Z*)-7-(2,5-Dimethoxy-3-nitrophenyl)-3-[(4-methoxybenzyloxy)-4-methyl-hept-4-en-2-yl]-2,2-dimethyl-1,3-dioxolane (3.34 3.34)

Vinyl bromide **3.39** (110 mg, 0.275 mmol, 100 mol %) and pinacol ester **3.40** (139 mg, 0.413 mmol, 150 mol %) were added to a resealable pressure tube (13 x 100 mm) and dissolved in THF (1.05 mL, 0.26 M). Degassed aqueous NaOH solution (0.1 mL, 0.825 mmol, 300 mol %, 3 M) was added and after additional degassing of the reaction mixture, Pd(dppf) Cl_2 · DCM (23 mg, 0.028 mmol, 10 mol %) was added. The mixture was stirred under argon at 50°C for 25 h. The black reaction mixture was diluted with DCM (3 mL)

and aqueous saturated $NaHCO_3$ solution (3 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 3 mL), the combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Flash column chromatography (SiO_2, 10–20% EtOAc/hexanes) furnished the title compound **3.34** (109 mg, 0.206 mmol, 75% yield) as a yellow oil.

R_f = 0.32 (SiO_2, hexanes/EtOAc = 5 : 1).

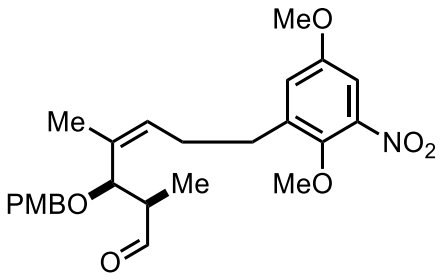
$[\alpha]_{27}^{D}$= +17.5 (c = 1.55, $CHCl_3$ 92% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): major diastereoisomer, *dr* = 5 : 1, δ 7.21–7.19 (m, 2H), 7.15 (d, *J* = 3.2 Hz, 1H), 6.93 (d, *J* = 3.1 Hz, 1H), 6.86–6.84 (m, 2H), 5.43 (t, *J* = 7.2 Hz, 1H), 4.30 (d, *J* = 11.3 Hz, 1H), 4.11 (d, *J* = 5.6 Hz, 1H), 4.05 (d, *J* = 11.2 Hz, 1H), 4.04–3.95 (m, 1H), 3.86–3.83 (m, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.58 (t, *J* = 7.9 Hz, 1H), 2.78–2.64 (m, 2H), 2.46–2.36 (m, 1H), 2.30–2.20 (m, 1H), 1.91 (dqd, *J* = 6.9 Hz, 5.9 Hz, 6.7 Hz, 1H) 1.73 (d, *J* = 0.7 Hz, 3H), 1.35 (s, 3H), 1.30 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 154.8, 145.4, 143.9, 139.0, 135.8, 130.6, 129.0, 127.9, 121.6, 113.6, 108.0, 106.6, 77.5, 76.6, 70.0, 66.5, 62.6, 55.7, 55.1, 40.5, 30.0, 28.0, 26.4, 25.3, 19.5, 10.0 ppm.

FTIR (ATR): 2982 (m), 2936 (m), 1613 (m), 1531 (s), 1456 (s), 1368 (m), 1235 (s), 1052 (vs) cm^{-1}.

HRMS (CI): Calcd. for $C_{29}H_{40}NO_8$ (MH^+): 530.2754; Found: 530.2745.



(*2R,3R,4Z*)-7-(2,5-Dimethoxy-3-nitrophenyl)-3-(4-methoxybenzyloxy)-2,4-dimethyl-hept-4-enal (3.35)

Acetonide **3.34** (1.52 g, 2.87 mmol, 100 mol %) was dissolved in EtOAc (78 mL, 0.04 M). This solution was added to a suspension of H_5IO_6 (1.31 g, 5.74 mmol, 200 mol %) in EtOAc (78 mL, 0.04 M) at 25 °C. The reaction mixture was stirred for 40 min (color change) at 25 °C, then $Na_2S_2O_3$ (one spatula) was added and the resulting mixture was stirred for a further 5 min at 25 ºC. The suspension was filtered through a plug of Celite/SiO_2 = 4:1 and the solvent was removed under reduced pressure (to furnish aldehyde **3.35** (1.30 g, 2.84 mmol, 99% yield) as a yellow oil. (Note: Aldehyde **3.35** is highly unstable and epimerizes easily at elevated temperatures and/or catalytic amounts of acid)

R_f = 0.26 (SiO_2, hexanes/EtOAc = 5 : 1).

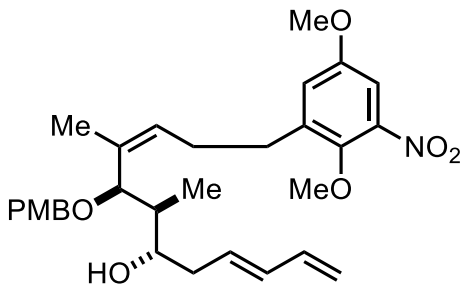
$[\alpha]_{26}^{D}$= +16 (c = 0.83, $CHCl_3$ 95% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56 (d, *J* = 2.1 Hz, 1H), 7.21–7.18 (m, 2H), 7.16 (d, *J* = 3.1 Hz, 1H), 6.94 (d, *J* = 3.2 Hz, 1H), 6.88–6.85 (m, 2H), 5.53 (t, *J* = 7.2 Hz, 1H), 4.34 (d, *J* = 11.3 Hz, 1H), 4.29 (d, *J* = 8.4 Hz, 1H), 4.06 (d, *J* = 11.3 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 2.74–2.64 (m, 3H), 2.41–2.32 (m, 1H), 2.30–2.22 (m, 1H), 1.73 (d, *J* = 1.0 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 203.1, 159.2, 154.0, 145.5, 143.0, 138.9, 133.6, 130.1, 129.0, 129.3, 121.6, 113.7, 106.9, 75.8, 69.4, 62.7, 55.8, 55.2, 49.6, 30.1, 28.2, 18.5, 10.7 ppm.

FTIR (ATR): 2939 (m), 2838 (m), 1723 (m), 1531 (s), 1514 (s), 1368 (m), 1236 (s), 1053 (s) cm^{-1}.

HRMS (CI): Calcd. for $C_{25}H_{31}NO_7$ (M^+): 457.2101; Found: 457.2094.



(*3E*,*6R*,*7S*,*8R*,*9Z*)-12-(2,5-dimethoxy-3-nitrophenyl)-8-(4-methoxybenzyloxy)-7,9-dimethyldodeca-1,3,9-trien-6-ol (3.36)

A solution of Me_2AlCl in hexanes (5.7 mL, 5.7 mmol, 250 mol %, 1.0 M) was added dropwise (over glass wall) at –78 °C to a stirred solution of aldehyde **3.35** (1.05 g, 2.29 mmol, 100 mol %) in DCM (11.5 mL, 0.2 M). After 10 min penta-1,3-dienyltrimethyl silane[122] (964 mg, 6.87 mmol, 300 mol %) was added dropwise (over glass wall) at –78 °C and the dark orange solution was stirred for a further 5 h at this temperature. Phosphate buffer (pH = 7) was added (15 mL) followed by a concentrated citric acid solution (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The solvent was removed under reduced pressure after drying

over Na_2SO_4 and filtration. Flash column chromatography (SiO_2, 10–20% EtOAc/hexanes) furnished the title compound **3.36** (635 mg, 1.209 mmol, 53% yield, >20 : 1 *dr*) as a yellow oil. . The stereochemical assignment was inferred based on analogy with the literature precedent.[113]

R_f = 0.46 (SiO_2, hexanes/EtOAc = 2 : 1).

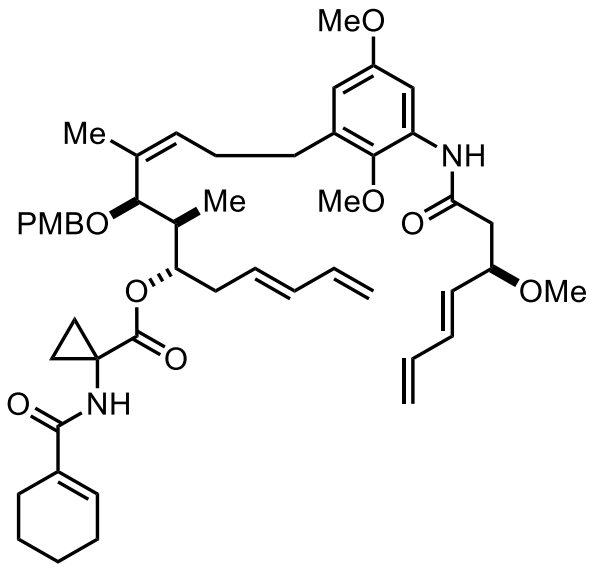
$[\alpha]_{25}^{D}$= +95.4 (c = 1.00, $CHCl_3$ 92% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.19 (m, 2H), 7.15 (d, *J* = 3.2 Hz, 1H), 6.93 (d, *J* = 3.2 Hz, 1H), 6.88–6.85 (m, 2H), 6.27 (dt, *J* = 17.0 Hz, 10.4 Hz, 1H), 6.05 (dd, *J* = 15.0 Hz, 10.4 Hz, 1H), 5.67 (dt, *J* = 15.2 Hz, 7.4 Hz, 1H), 5.45 (t, *J* = 7.2 Hz, 1H), 5.07 (dd, *J* = 17.0 Hz, 1.1 Hz, 1H), 4.96 (dd, *J* = 10.3 Hz, 1.5 Hz, 1H), 4.32 (d, *J* = 11.3 Hz, 1H), 4.26 (d, *J* = 5.4 Hz, 1H), 4.04 (d, *J* = 11.3 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.55 (ddt, *J* = 7.4 Hz, 5.4 Hz, 5.3 Hz, 1H), 2.76–2.68 (m, 2H), 2.64 (d, *J* = 5.2 Hz, 1H), 2.41 (sext, *J* = 7.7 Hz, 1H), 2.30–2.22 (m, 1H), 2.18–2.12 (m, 2H), 1.82–1.74 (m, 1H), 1.76 (d, *J* = 1.0 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 154.9, 145.4, 144.0, 138.9, 136.8, 135.2, 133.4, 131.2, 130.0, 129.4, 128.7, 121.6, 115.5 113.7, 106.7, 77.7, 73.4, 69.0, 62.6, 55.7, 55.1, 41.7, 37.6, 30.1, 28.2, 19.7, 12.0 ppm.

FTIR (ATR): 3476 (OH, br), 3083 (w), 2939 (m), 2837 (m), 1613 (m), 1531 (vs), 1514 (s), 1236 (s), 1053 (s) cm^{-1}.

HRMS (CI): Calcd. for $C_{30}H_{39}NO_7$ (M^+): 525.2727; Found: 525.2717.



(*3E*,*6S*,*7S*,*8R*,*9Z*)-12-(2,5-dimethoxy-3-[(*3R*,*4E*)-3-methoxyhepta-4,6-dienamido]phenyl)-8-(4-methoxybenzyloxy)-7,9-dimethyldodeca-1,3,9-trien-6-yl 1-[(cyclohex-1-ene)amido]cyclopropane-1-carboxylate (3.55)

Sulfur (156 mg, 4.88 mmol, 3500 mol %) and $NaBH_4$ (105 mg, 2.78 mmol, 2000 mol %) were added at 25 °C to a stirred solution of nitroarene **3.36** (100 mg, 0.139 mmol, 100 mol %) in THF (14 mL, 0.01 M). This solution was stirred under inert conditions for a further 1 h at 50 °C. After cooling to 25 °C saturated $NaHCO_3$ solution (15 mL) was slowly added, the layers separated and the aqueous layer was extracted with chloroform (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and filtered. Then the solvent was removed in vacuo and the crude solid residue was used in the next step.

Freshly distilled ethyldiisopropylamine (898 mg, 6.95 mmol, 5000 mol %) was added to a solution of solid residue in toluene (14 mL, 0.01 M) at 25 °C. This solution was added at 25 °C to a stirred solution of acid **1.64** (109 mg, 0.698 mmol, 500 mol %) and BOPCl

(212 mg, 0.834 mmol, 600 mol%) in THF (23 mL, 0.03 M with respect to acid **1.64**). After addition of powdered molecular sieves (4 Å, 2 spatulas) the reaction mixture was stirred for further 21 h at 25 °C under inert conditions. Saturated $NaHCO_3$ solution (45 mL) was added, the layers separated and the aqueous layer was extracted with chloroform (3 x 45 mL). The combined organic layers were dried ($MgSO_4$), filtered and then the solvent was removed in vacuo. Flash column chromatography (SiO_2, toluene/EtOAc/hexanes = 3 : 1 : 1) furnished bis(diene) **3.55** (79 mg, 0.096 mmol) in 69% yield as a yellow oil.

R_f = 0.10 (SiO_2, toluene/EtOAc/hexanes = 3 : 1 : 1).

$[\alpha]_{26}^{D}$= +34.1 (c = 1.00, $CHCl_3$ 90% *ee*).

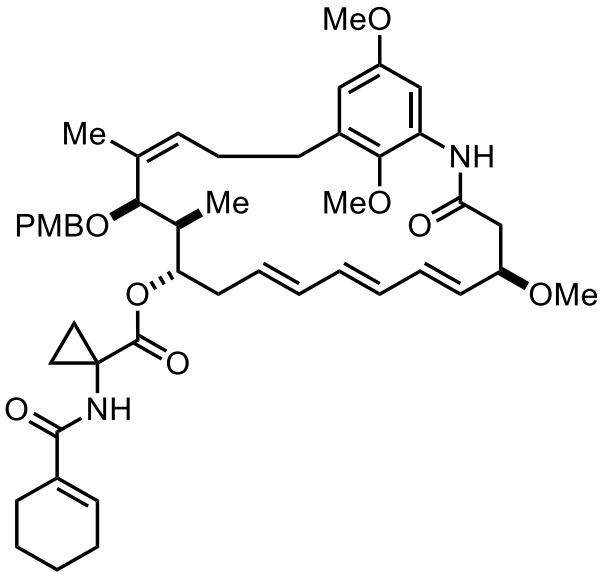
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 7.92 (d, *J* = 3.0 Hz, 1H), 7.21–7.19 (m, 2H), 6.85–6.83 (m, 2H), 6.57–6.55 (m, 1H), 6.43 (d, *J* = 3.0 Hz, 1H), 6.33 (dt, *J* = 16.4 Hz, 10.4 Hz, 1H), 6.30 (dd, *J* = 21.2 Hz, 10.8 Hz, 1H), 6.24 (dt, *J* = 17.0 Hz, 10.2 Hz, 1H), 6.17 (s, 1H), 5.98 (dd, *J* = 15.2 Hz, 10.3 Hz, 1H), 5.56 (ddd, *J* = 20.3 Hz, 14.3 Hz, 8.0 Hz, 1H), 5.55–5.48 (m, 2H), 5.28 (d, *J* = 16.7 Hz, 1H), 5.17 (d, *J* = 9.6 Hz, 1H), 5.06 (d, *J* = 17.0 Hz, 1H), 4.96 (d, *J* = 10.1 Hz, 1H), 4.80 (ddd, *J* = 8.9 Hz, 4.8 Hz, 3.0 Hz, 1H), 4.28 (d, *J* = 11.3 Hz, 1H), 4.07 (td, *J* = 7.9 Hz, 3.9 Hz, 1H), 4.01 (d, *J* = 11.3 Hz, 1H), 3.91 (d, *J* = 8.1 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.68 (s, 3H), 3.37 (s, 3H), 2.69–2.60 (m, 4H), 2.43–2.35 (m, 1H), 2.30–2.05 (m, 8H), 1.76 (s, 4H), 1.67–1.60 (m, 2H), 1.59–1.54 (m, 2H), 1.50–1.47 (m, 2H), 1.14–1.10 (m, 2H), 0.98 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 169.2, 168.8, 159.0, 156.0, 140.8, 136.9, 135.7, 134.7, 134.4, 134.3 133.8, 133.5 133.3, 132.4, 131.3, 131.0, 130.1, 129.8, 129.2, 118.9,

115.6, 113.7, 110.6, 103.3, 78.7, 77.5, 75.1, 69.6, 61.2, 56.4, 55.5, 55.2, 44.2, 39.2, 33.9, 33.0, 30.1, 28.6, 25.4, 24.2, 22.1, 21.5, 18.8, 17.2, 11.0 ppm.

FTIR (ATR): 3311 (w, br), 2936 (m), 2245 (w), 1724 (m), 1667 (m), 1529 (m), 1513 (s), 1420 (m), 1171 (s), 1083 (s) cm^{-1}.

HRMS (CI): Calcd. for $C_{49}H_{65}N_2O_9$ ($M+H^+$): 825.4690; Found: 825.4695.



Cytotrienin A Core (3.56)

Indinylidene Grubbs-I derivative[124] (18 mg, 0.02 mmol, 20 mol %) was added to a solution of bisdiene **3.55** (79 mg, 0.096 mmol, 100 mol %) in DCM (60 mL, 1.6 mM) at 25 °C. The solution was then stirred at 40 °C under inert conditions in the dark. After 16 h additional ruthenium precatalyst (9 mg, 0.01 mmol, 10 mol %) was added, the mixture was sparged with argon, and stirred for 3 h at 40 °C. The solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, 30–50% EtOAc/hexanes) furnished the Cytotrienin A Core **3.56** (33 mg, 0.041 mmol) 43% yield as a yellow oil.

R_f = 0.22 (SiO_2, EtOAc/hexanes = 1 : 1).

$[\alpha]_{27}^{D}$= +51 (c = 1.00, $CHCl_3$ 90% *ee*).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.84 (d, *J* = 3.1 Hz, 1H), 7.19–7.17 (m, 2H), 6.85–6.83 (m, 2H), 6.59–6.56 (m, 1H), 6.38–6.31 (m, 1H), 6.33 (d, *J* = 3.1 Hz, 1H), 6.11 (s, 1H), 6.03–5.98 (m, 2H), 5.55 (dd, *J* = 15.6 Hz, 5.5 Hz, 1H), 5.49–5.46 (m, 2H), 4.81

(td, J = 6.9 Hz, 3.0 Hz, 1H), 4.31 (d, J = 11.2 Hz, 1H), 4.15–4.12 (m, 1H), 4.00 (d, J = 5.5 Hz, 1H), 3.97 (d, J = 11.2 Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.44 (s, 3H), 2.85–2.80 (m, 1H), 2.75–2.70 (m, 1H), 2.50–2.44 (m, 1H), 2.39–2.33 (m, 1H), 2.24–2.10 (m, 8H), 1.89–1.85 (m, 1H), 1.78 (d, J = 1.1 Hz, 3H), 1.66–1.63 (m, 3H), 1.59–1.57 (m, 3H), 1.30–1.20 (m, 3H), 0.98 (d, J = 6.9 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 169.3, 168.2, 158.9, 155.7, 140.6, 134.8, 134.2, 133.9, 133.5, 133.2, 133.0, 132.2, 131.0, 129.5, 129.3, 129.3, 129.2, 129.1, 113.7, 110.5, 103.1, 77.9, 75.3, 74.8, 70.1, 61.0, 56.9, 55.4, 55.3 43.6, 39.7, 33.9, 32.5, 31.2, 28.8, 25.4, 24.2, 22.1, 21.5, 19.3, 17.3, 17.1, 10.6 ppm.

FTIR (ATR): 3346 (w, br), 2934 (m), 1724 (m), 1667 (m), 1613 (m), 1514 (s), 1465 (m), 1247 (m), 1173 (s) cm^{-1}.

HRMS (ESI): Calcd. for $C_{47}H_{60}N_2O_9Na$ ($M+Na^+$): 819.4197; Found: 819.4187.

3.6 Spectra relevant to chapter 3

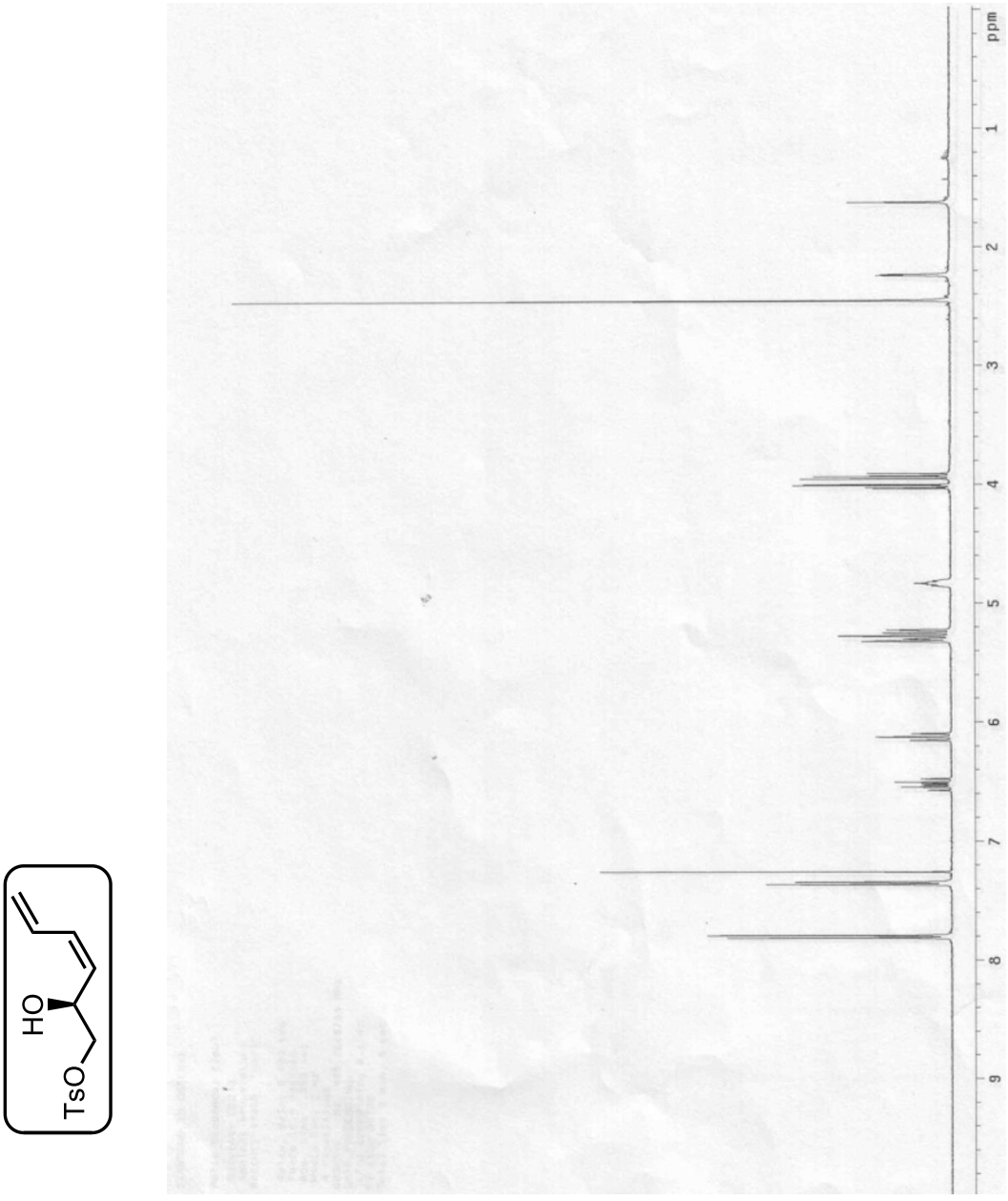


Figure 3.1 ^{1}H NMR spectrum of compound **3.19**

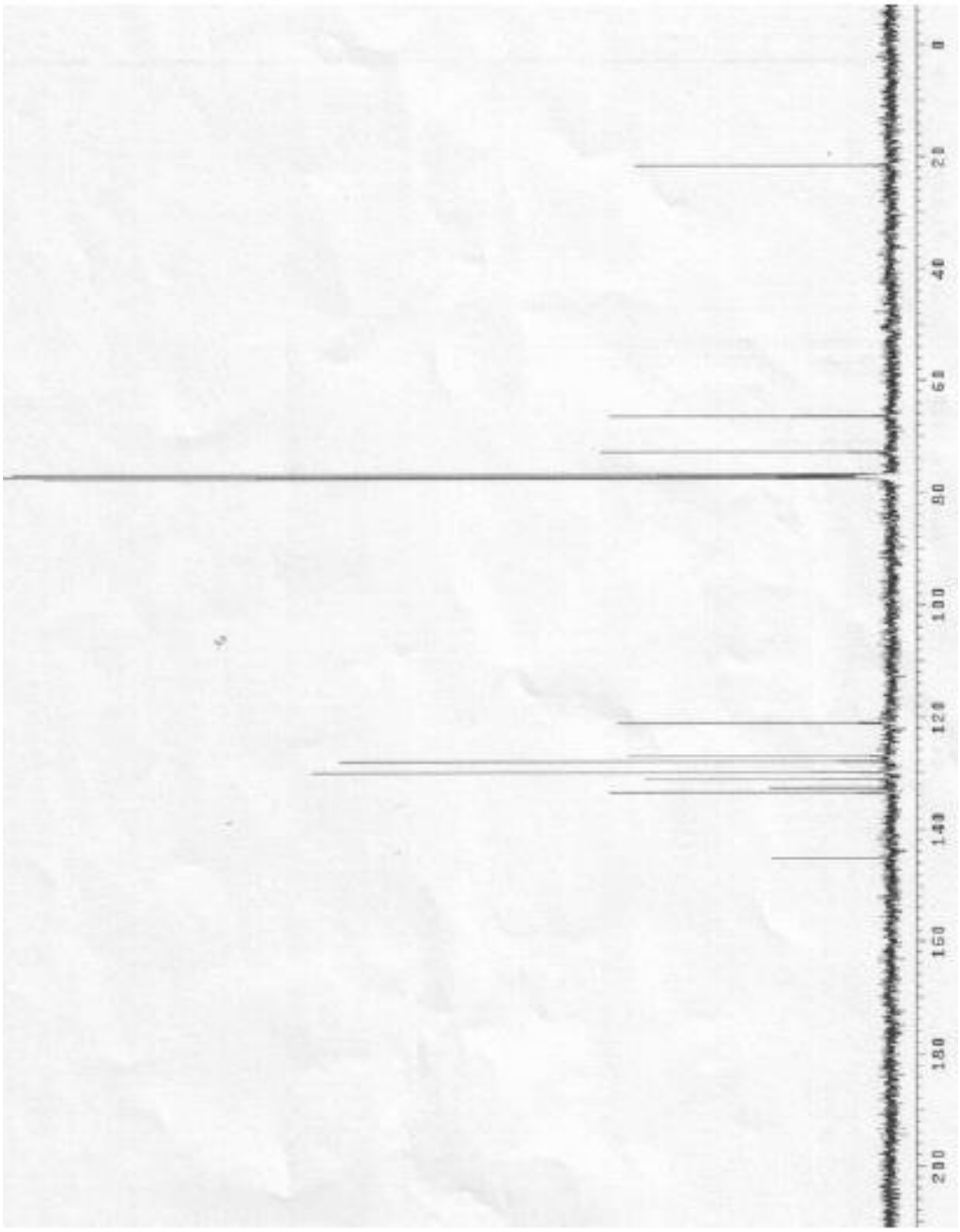


Figure 3.2 ^{13}C NMR spectrum of compound **3.19**

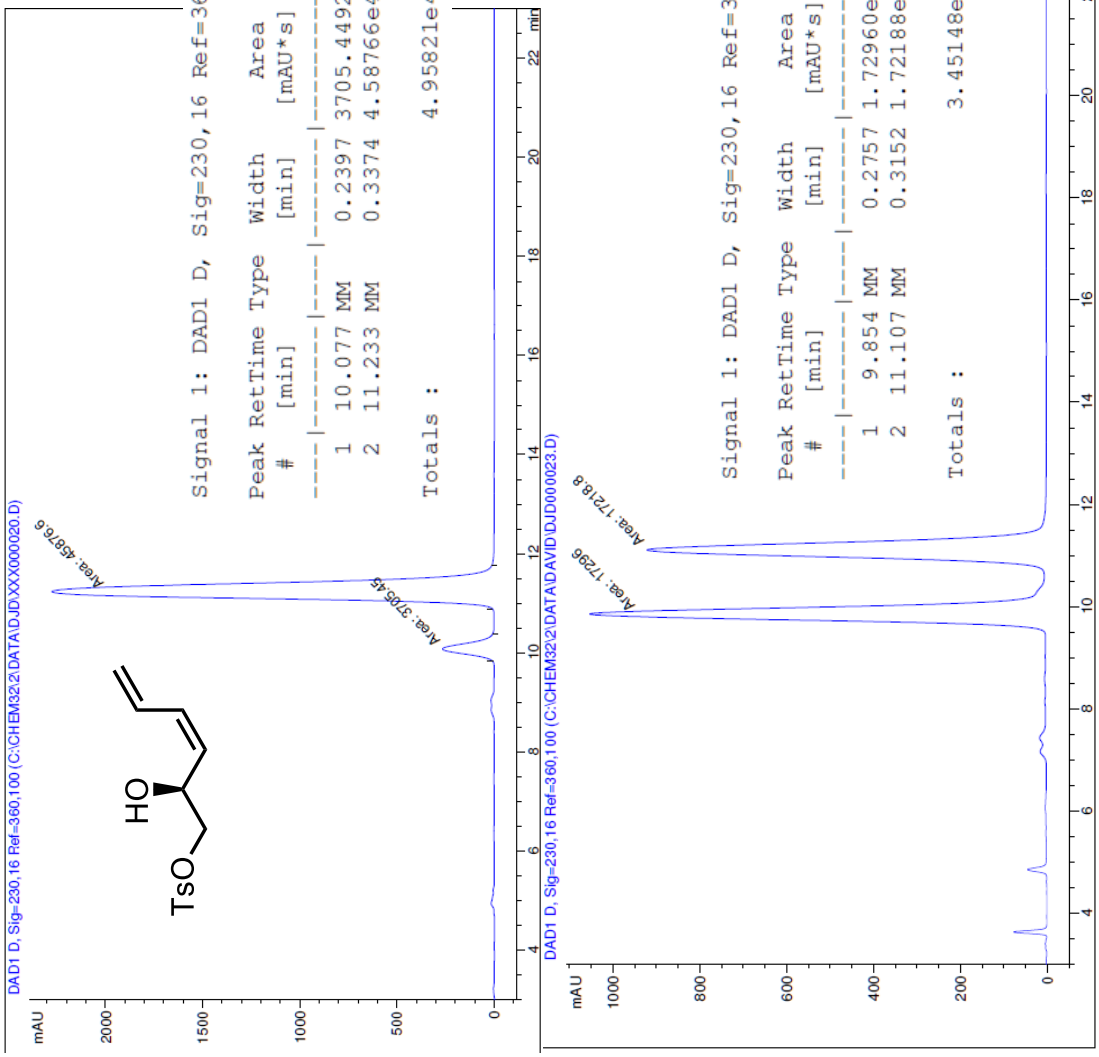


Figure 3.3 Chiral HPLC data for compound **3.19**

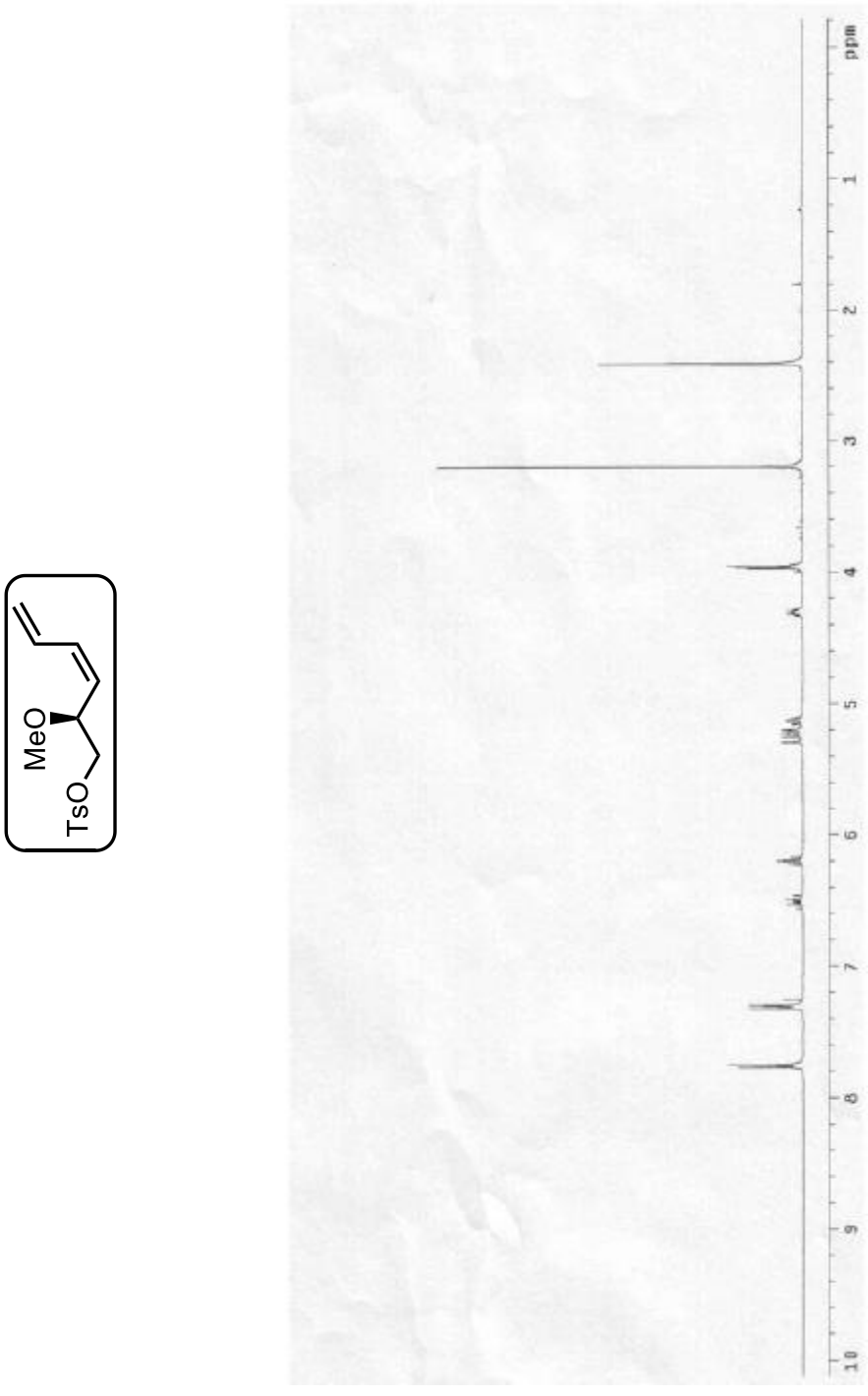


Figure 3.4 ^{13}C NMR spectrum of compound **3.20**

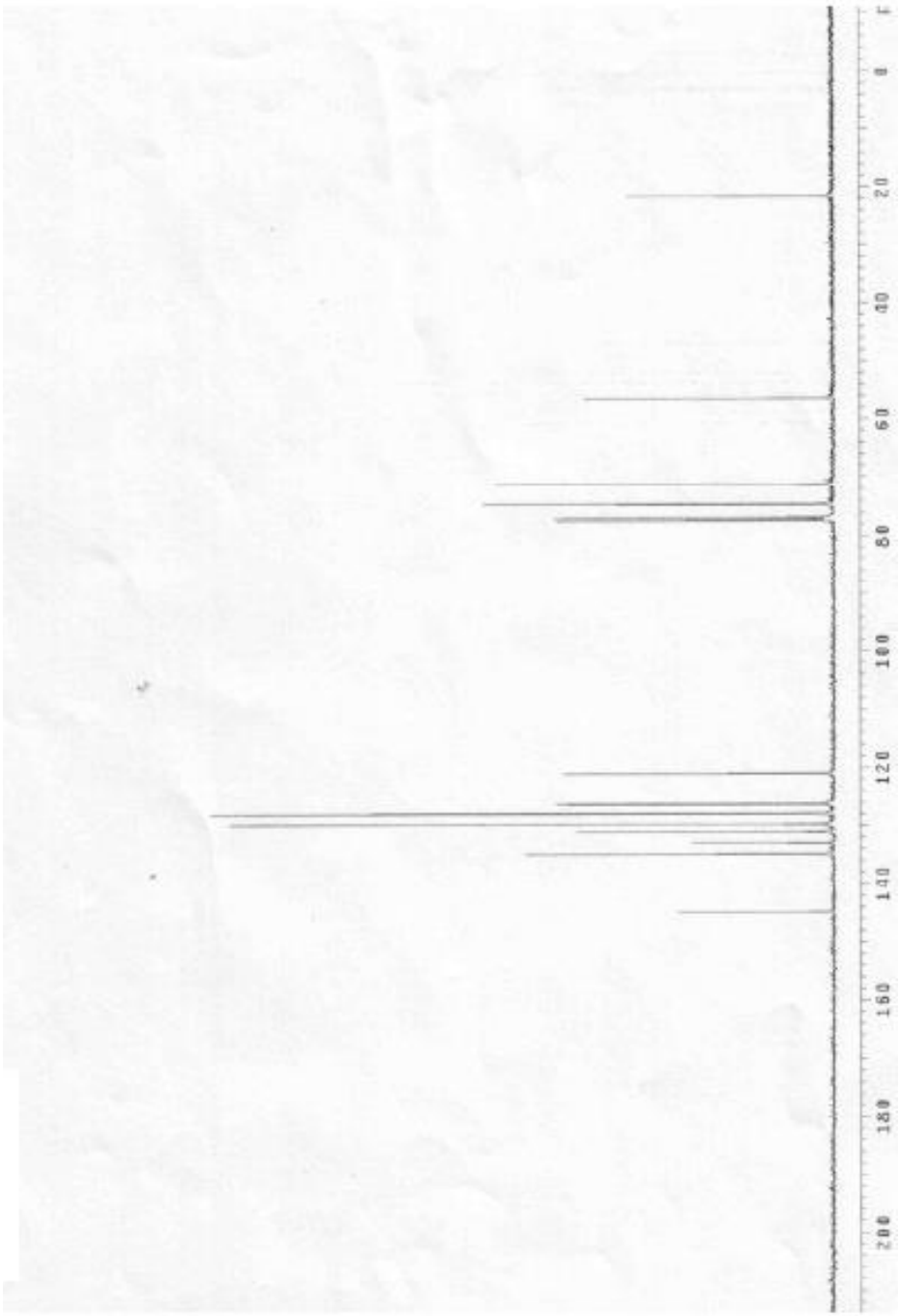


Figure 3.5 ^{13}C NMR spectrum of compound **3.20**

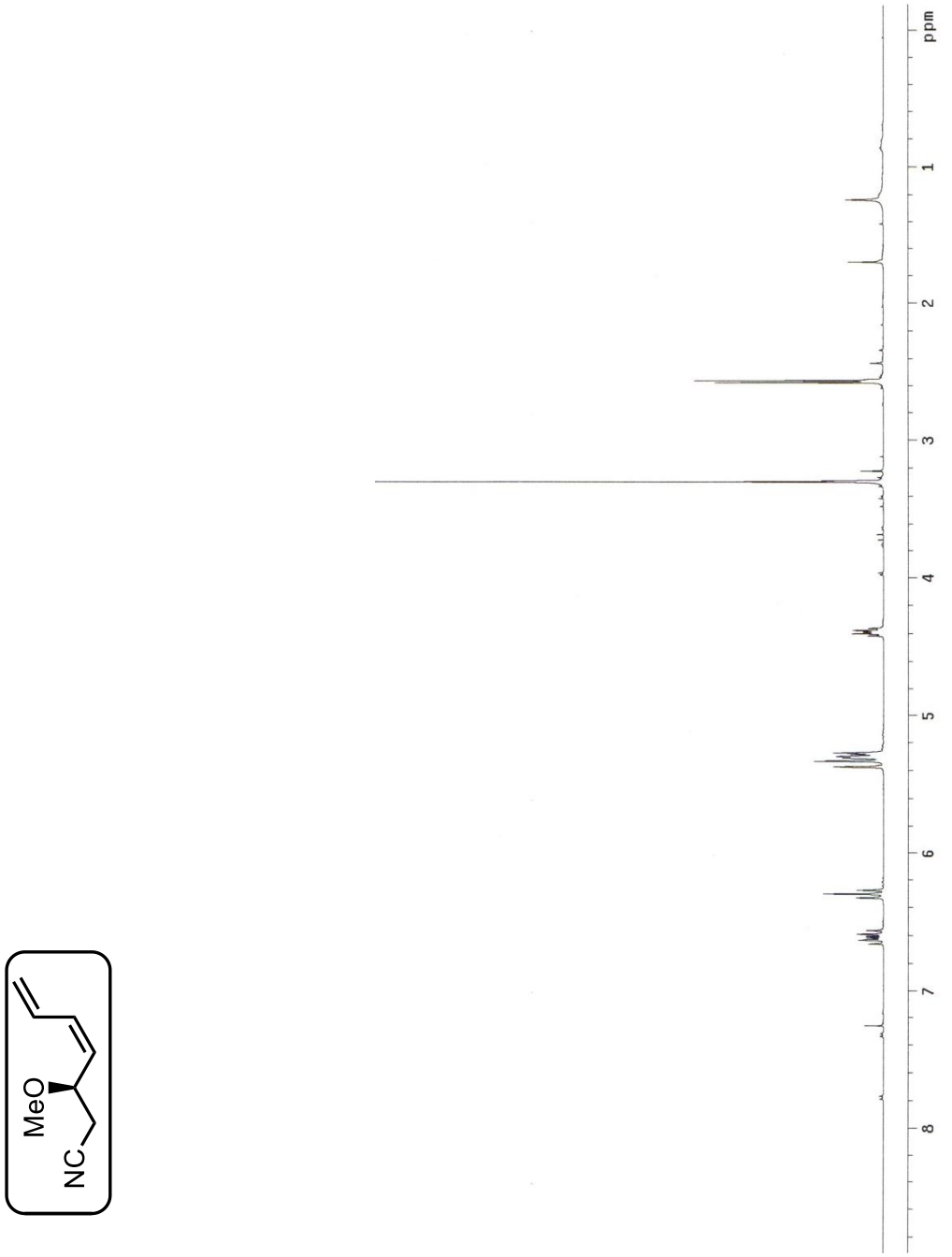


Figure 3.6 ^{1}H NMR spectrum of compound **3.21**

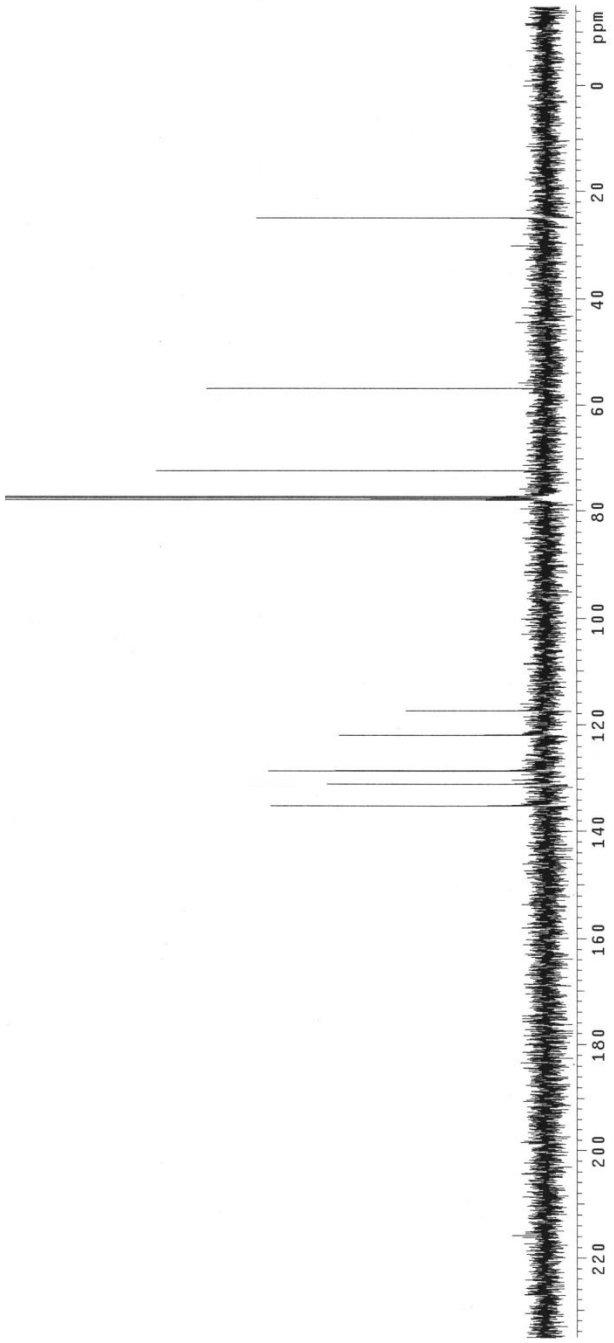


Figure 3.7 ^{13}C NMR spectrum of compound **3.21**

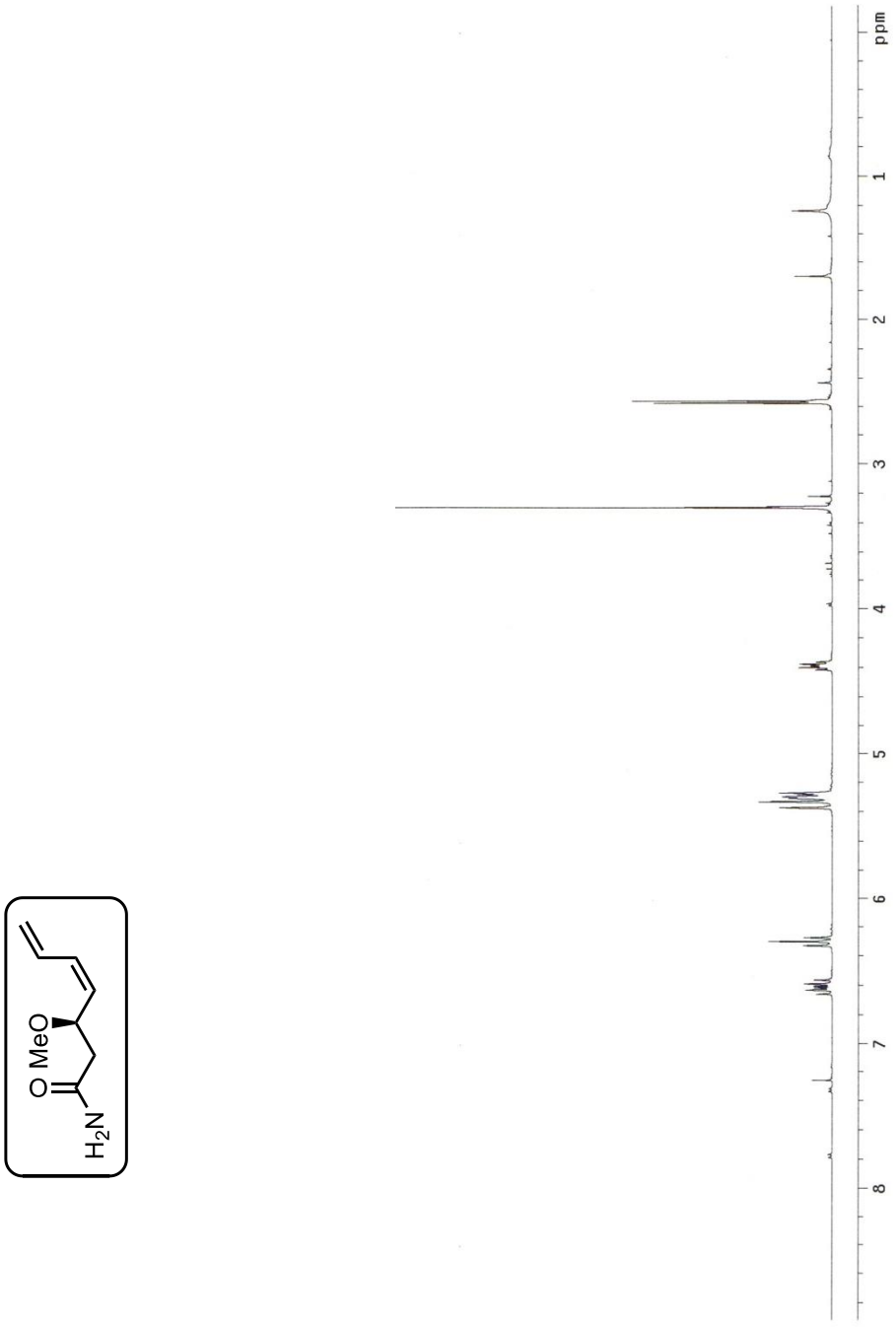


Figure 3.8 ^{1}H NMR spectrum of compound **3.22**

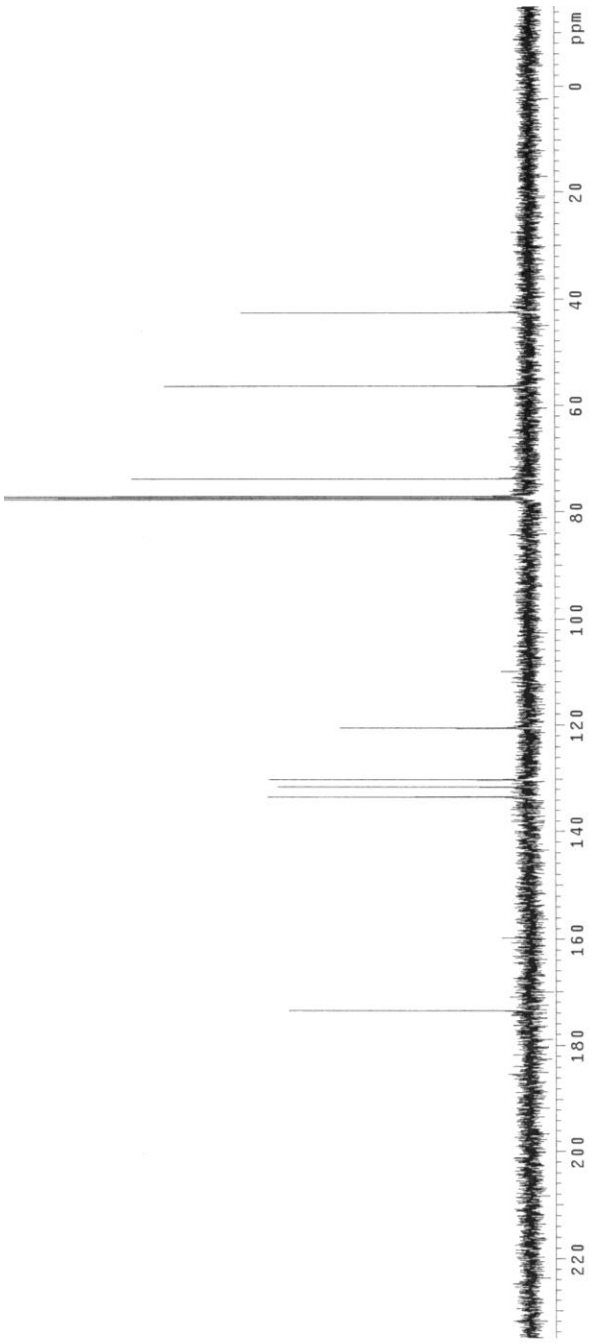


Figure 3.9 ^{13}C NMR spectrum of compound **3.22**

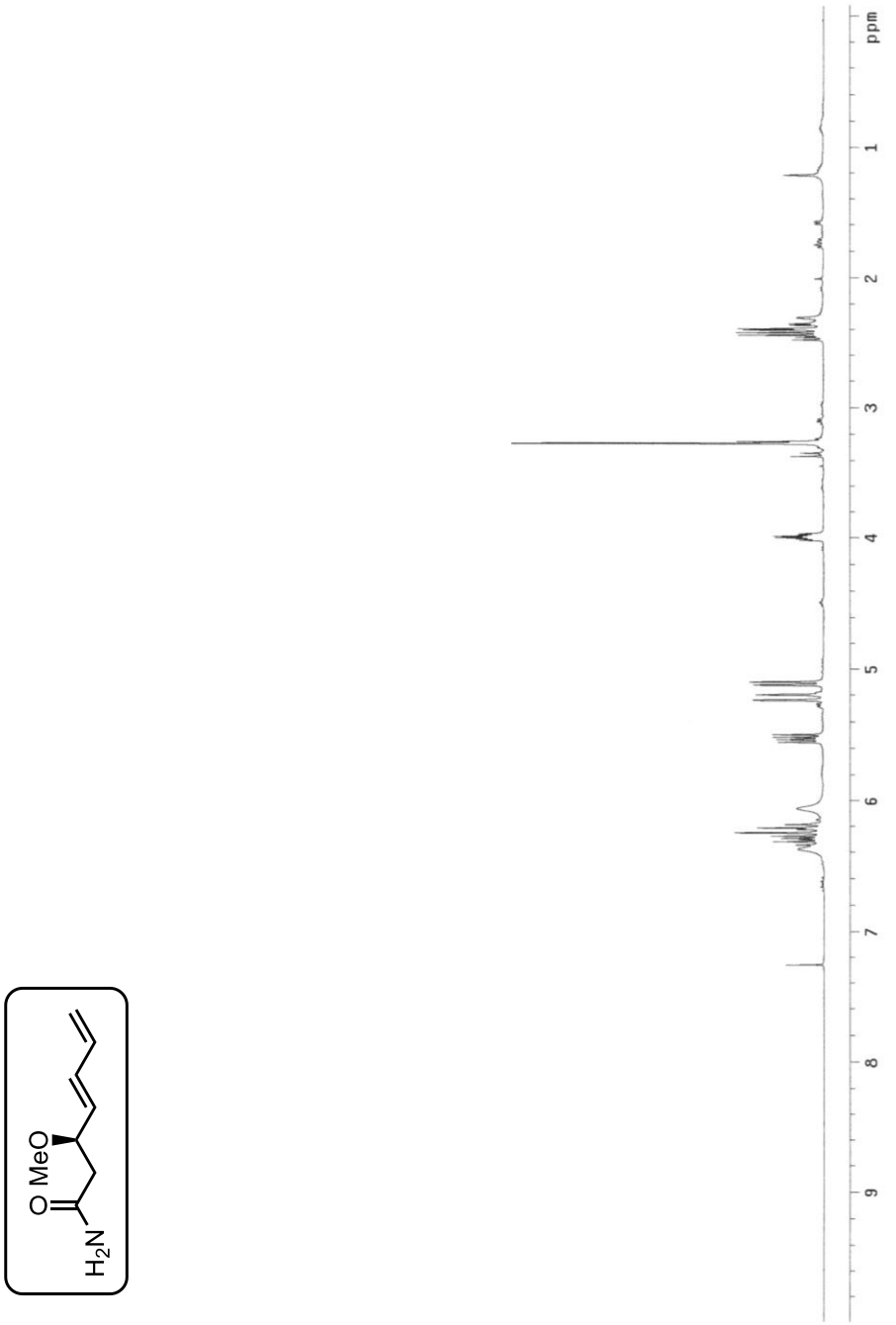


Figure 3.10 ^{1}H NMR spectrum of compound **3.23**

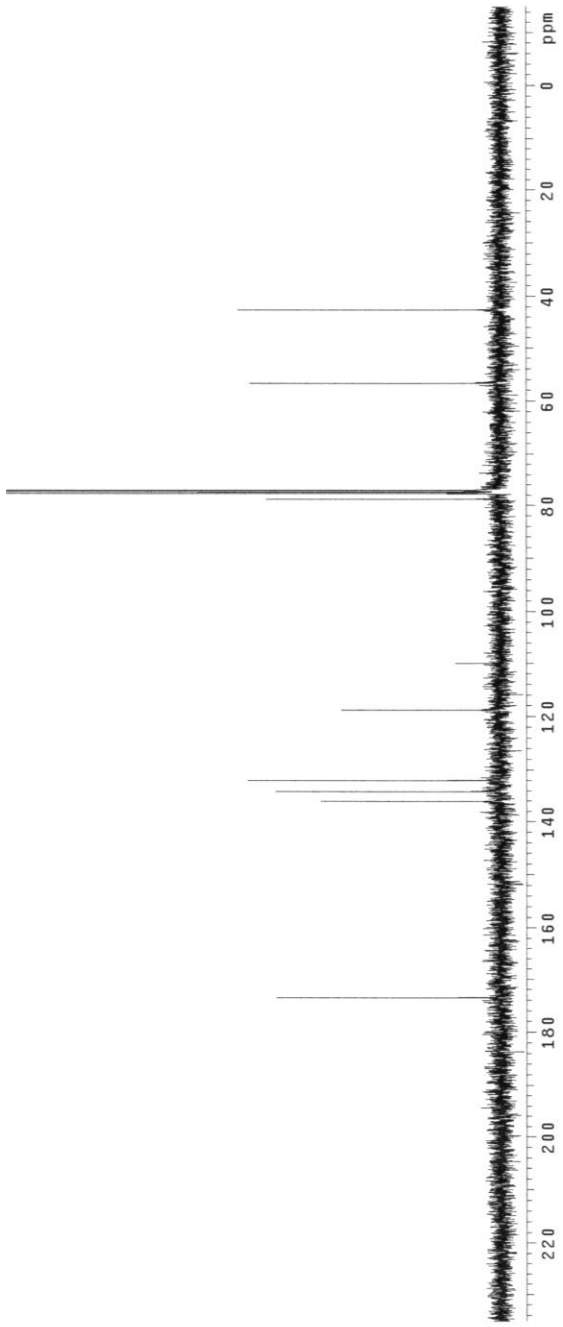


Figure 3.11 ^{13}C NMR spectrum of compound **3.23**

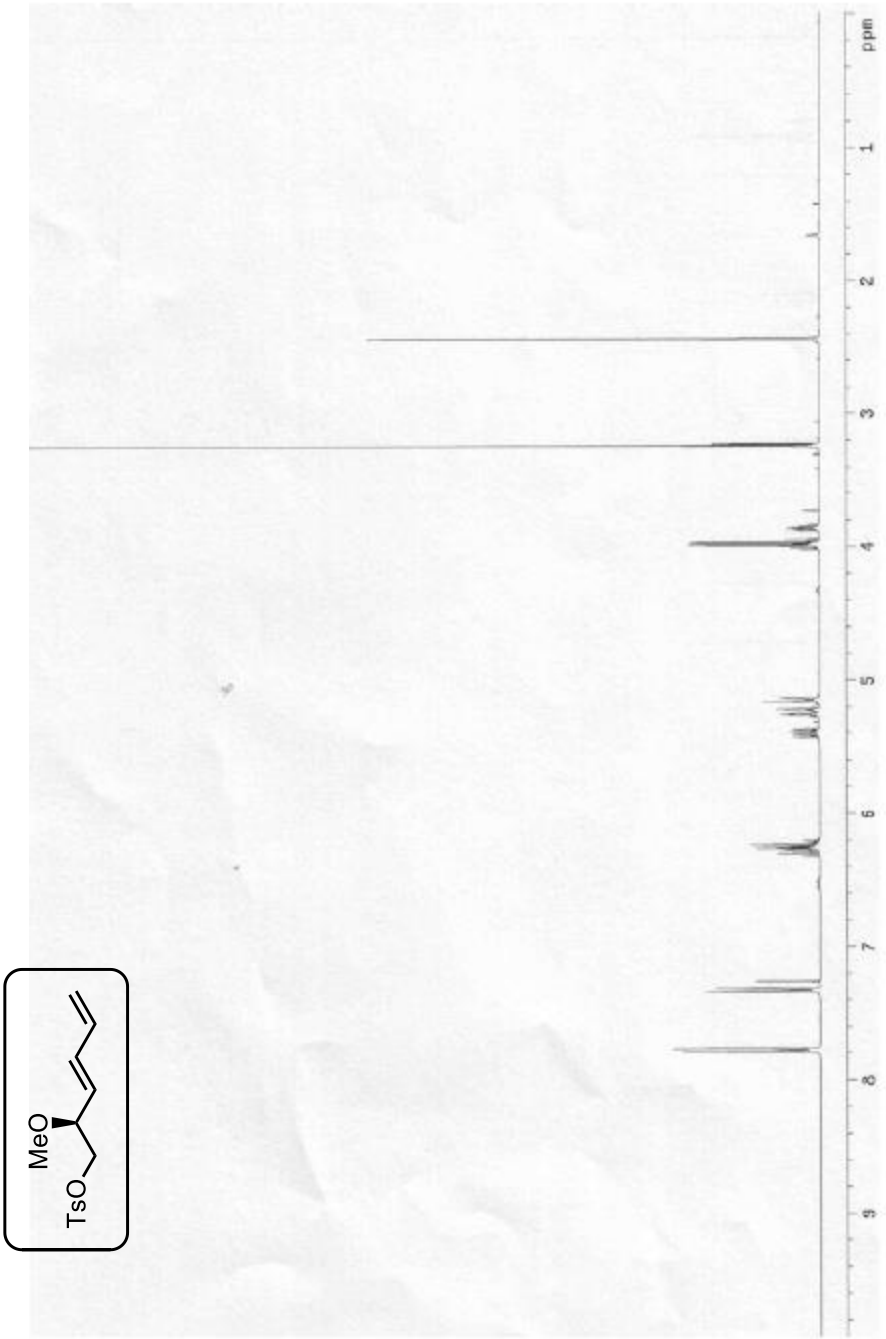


Figure 3.12 ^{1}H NMR spectrum of compound **3.3**

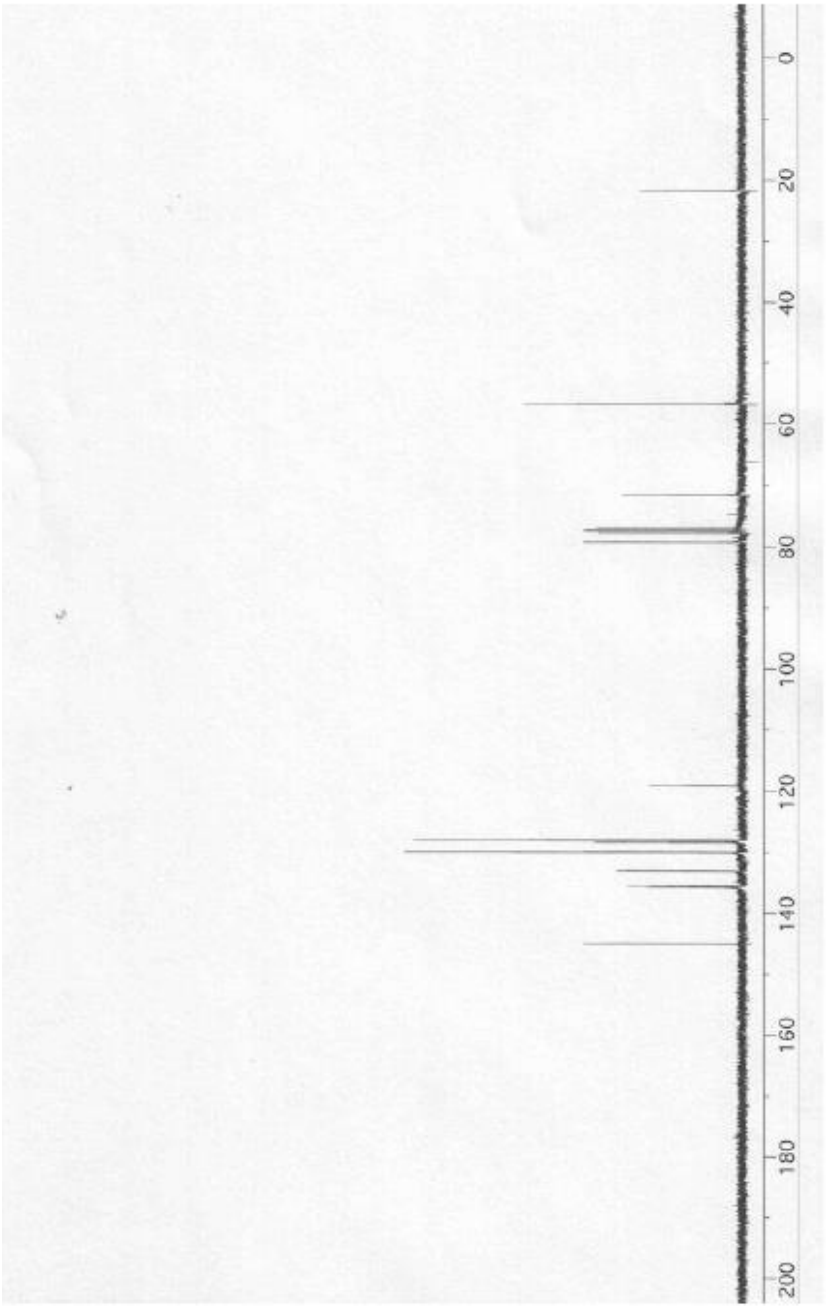


Figure 3.13 ^{13}C NMR spectrum of compound **3.3**

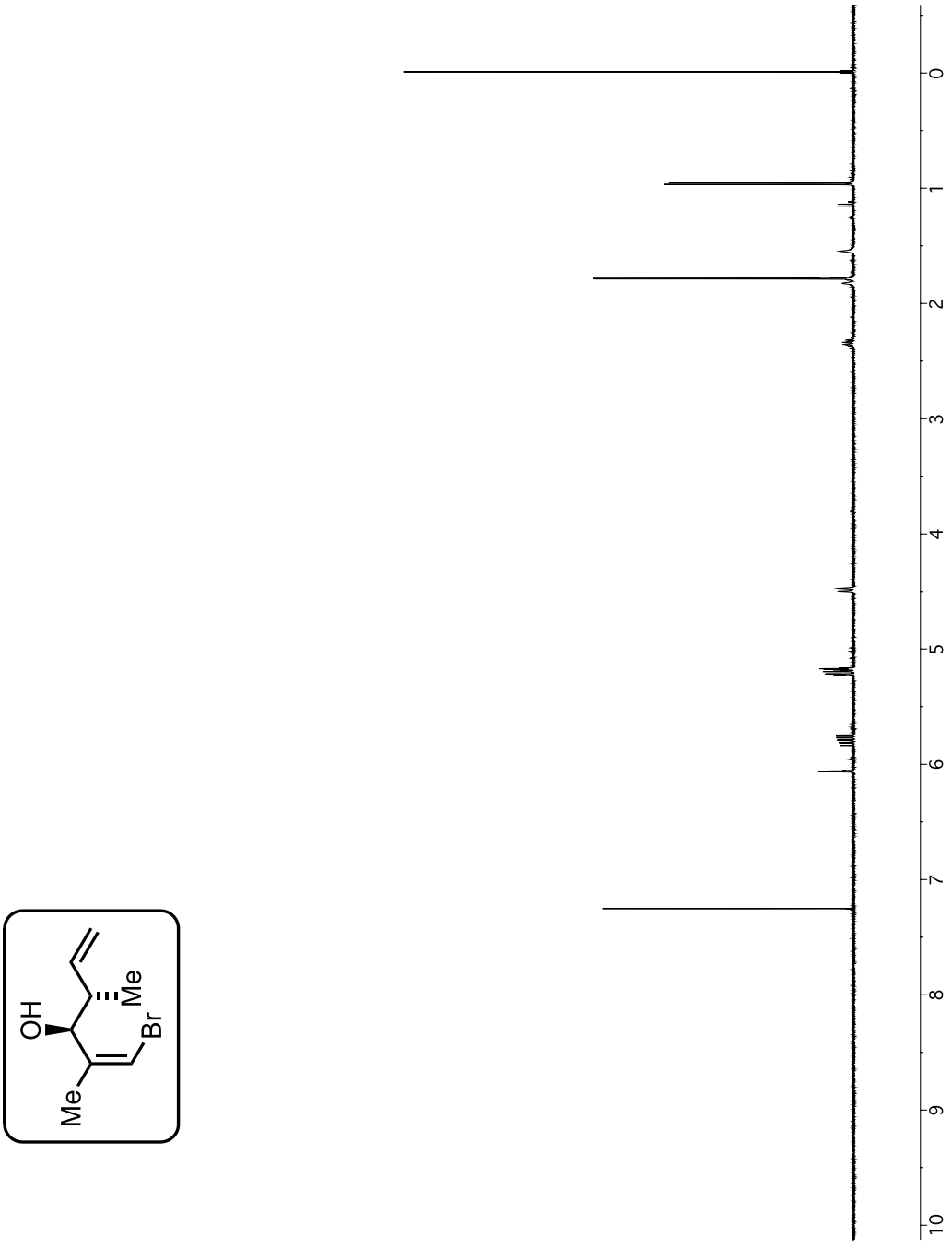


Figure 3.14 ^{1}H NMR spectrum of compound **3.14**

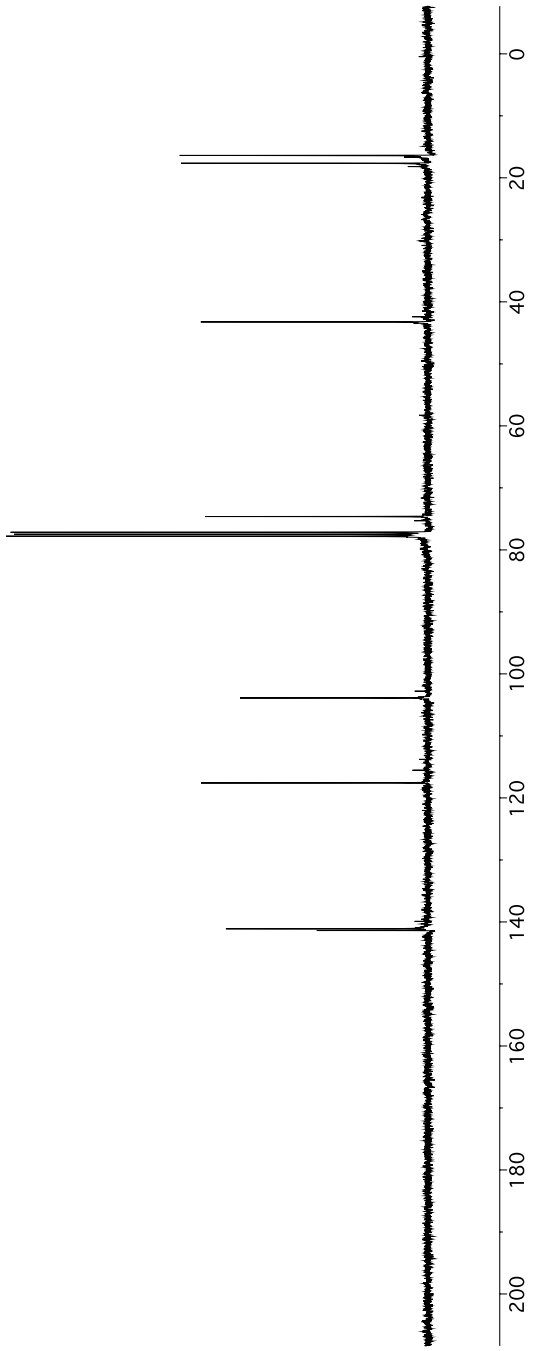


Figure 3.15 ^{13}C NMR spectrum of compound **3.14**

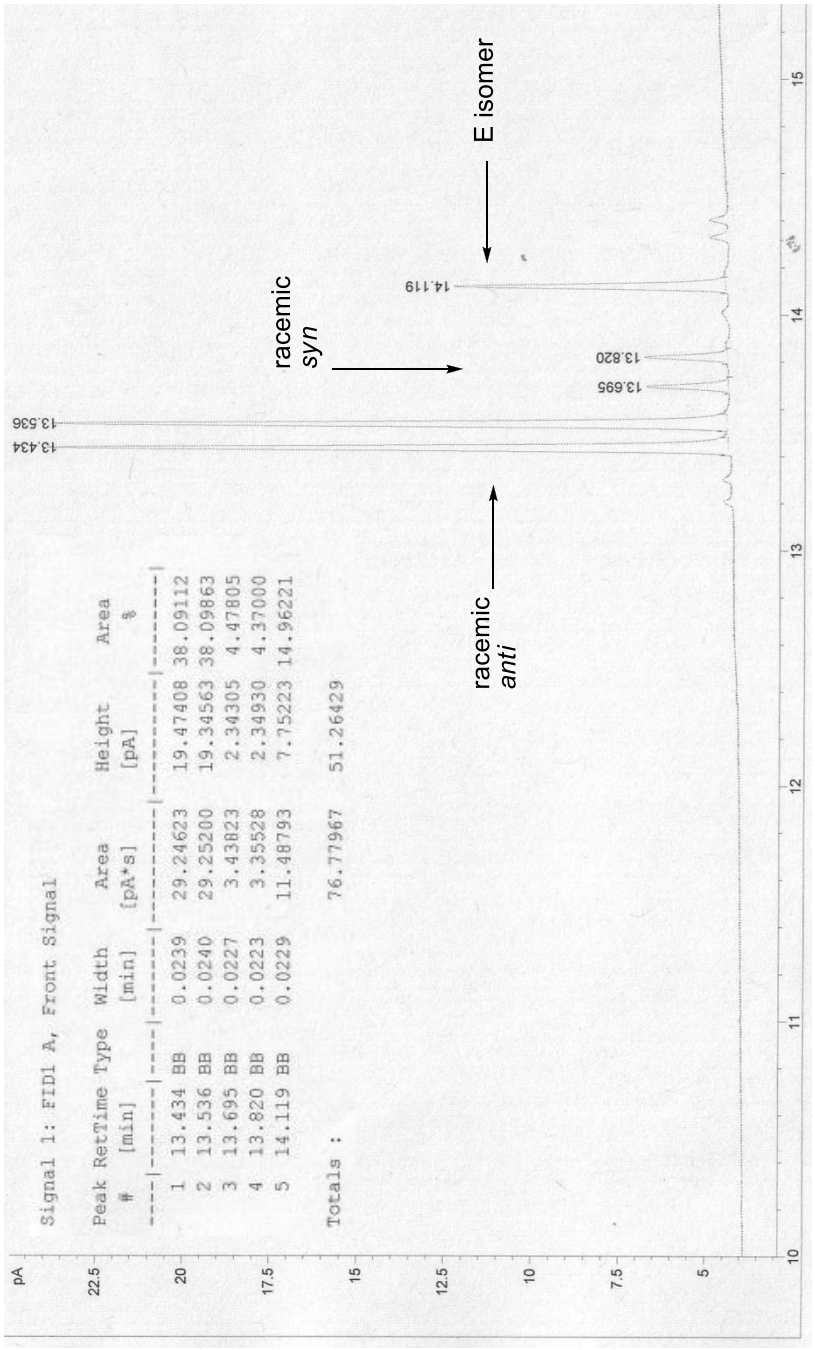


Figure 3.16 Racemic GC data for compound **3.14**

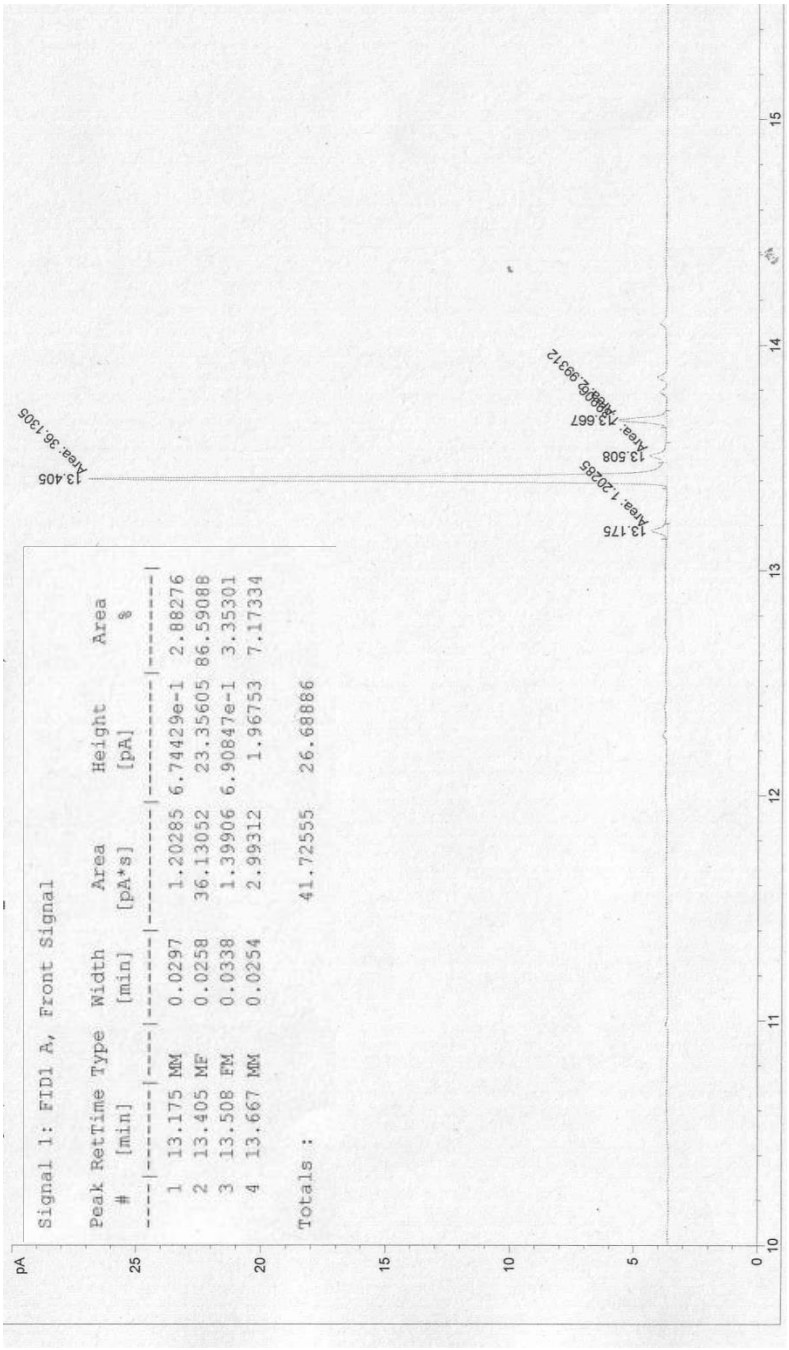
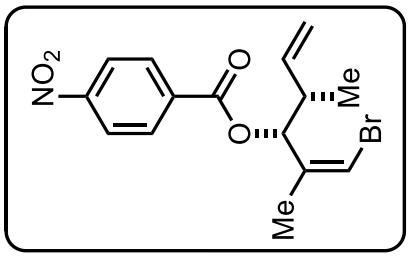


Figure 3.17 Chiral GC data for compound **3.14**



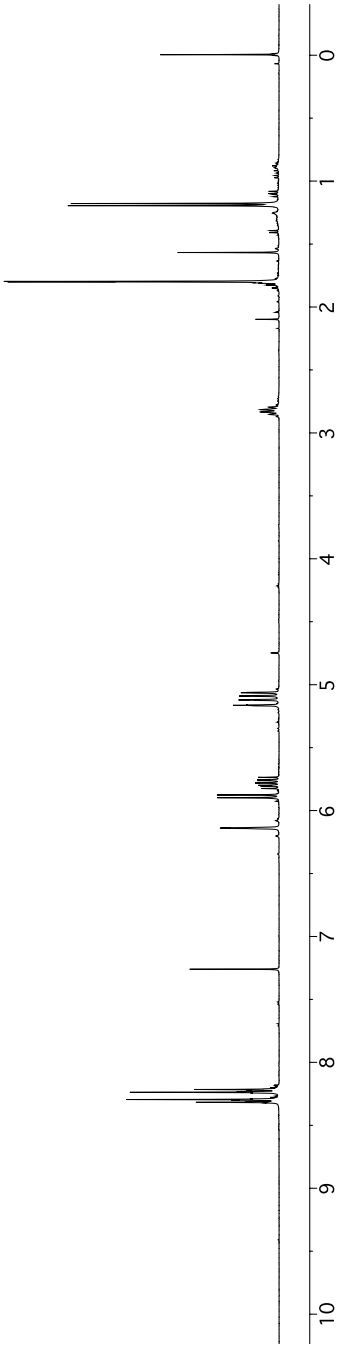


Figure 3.18 ^{1}H NMR spectrum of compound **3.29**

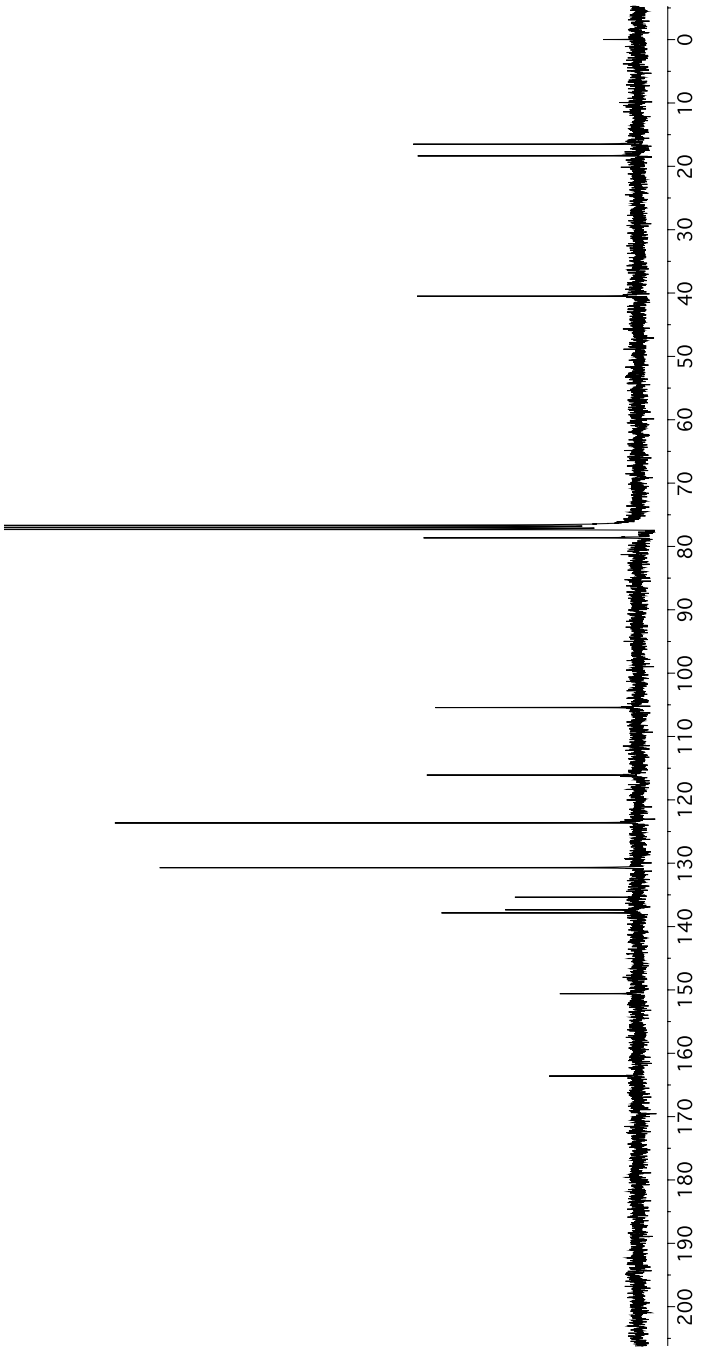


Figure 3.19 ^{13}C NMR spectrum of compound **3.29**

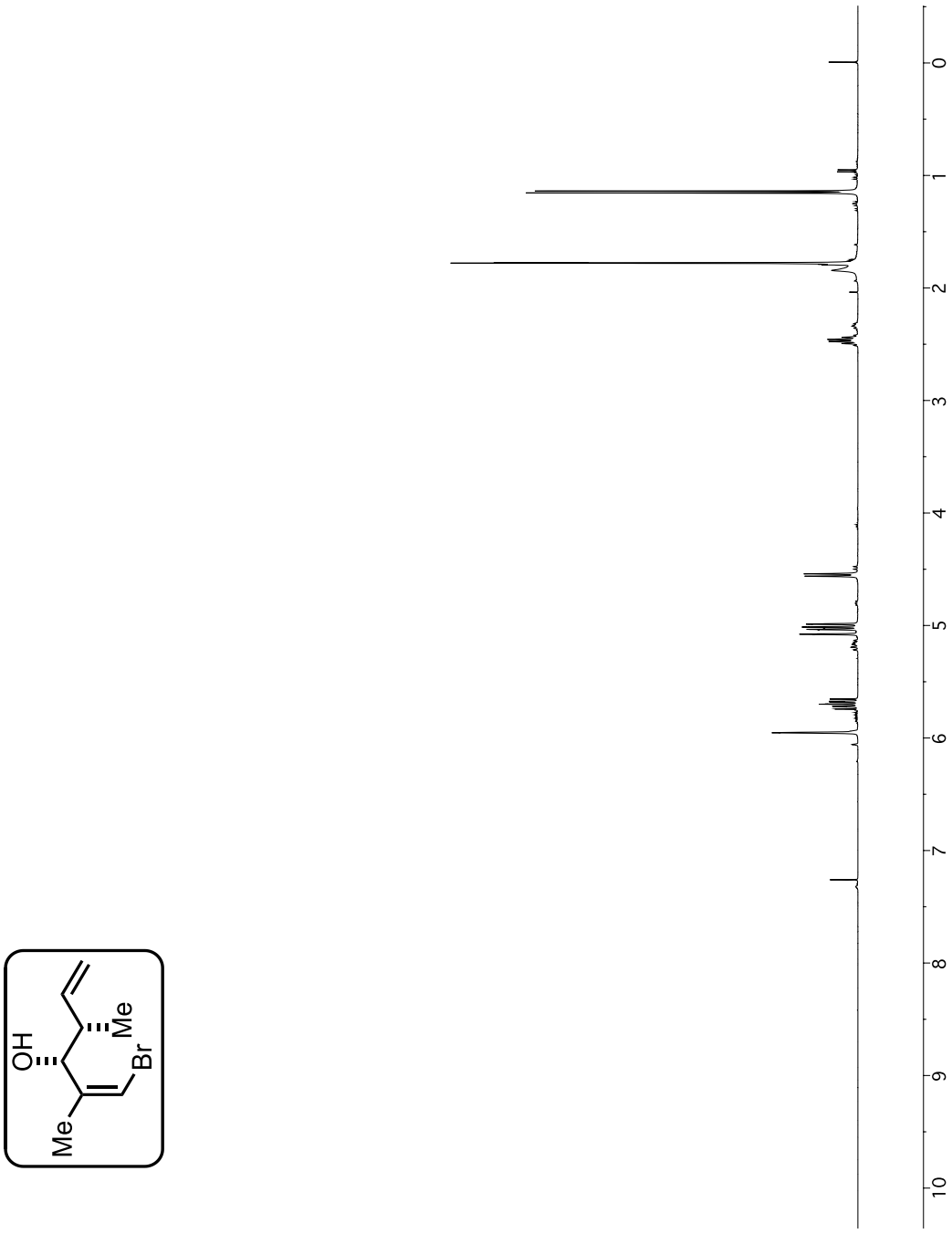


Figure 3.20 ^{1}H NMR spectrum of compound **3.30**

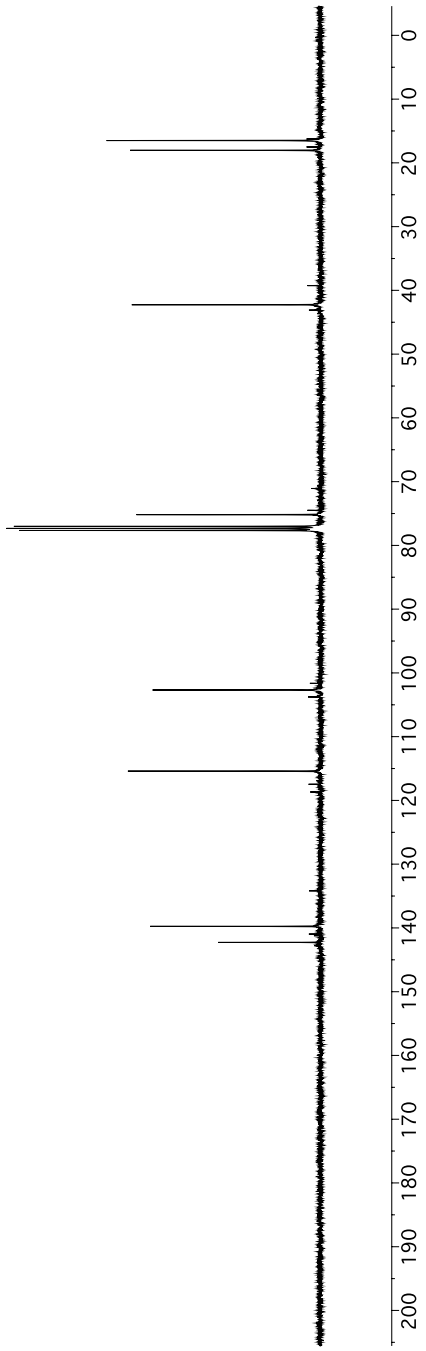


Figure 3.21 ^{13}C NMR spectrum of compound **3.30**

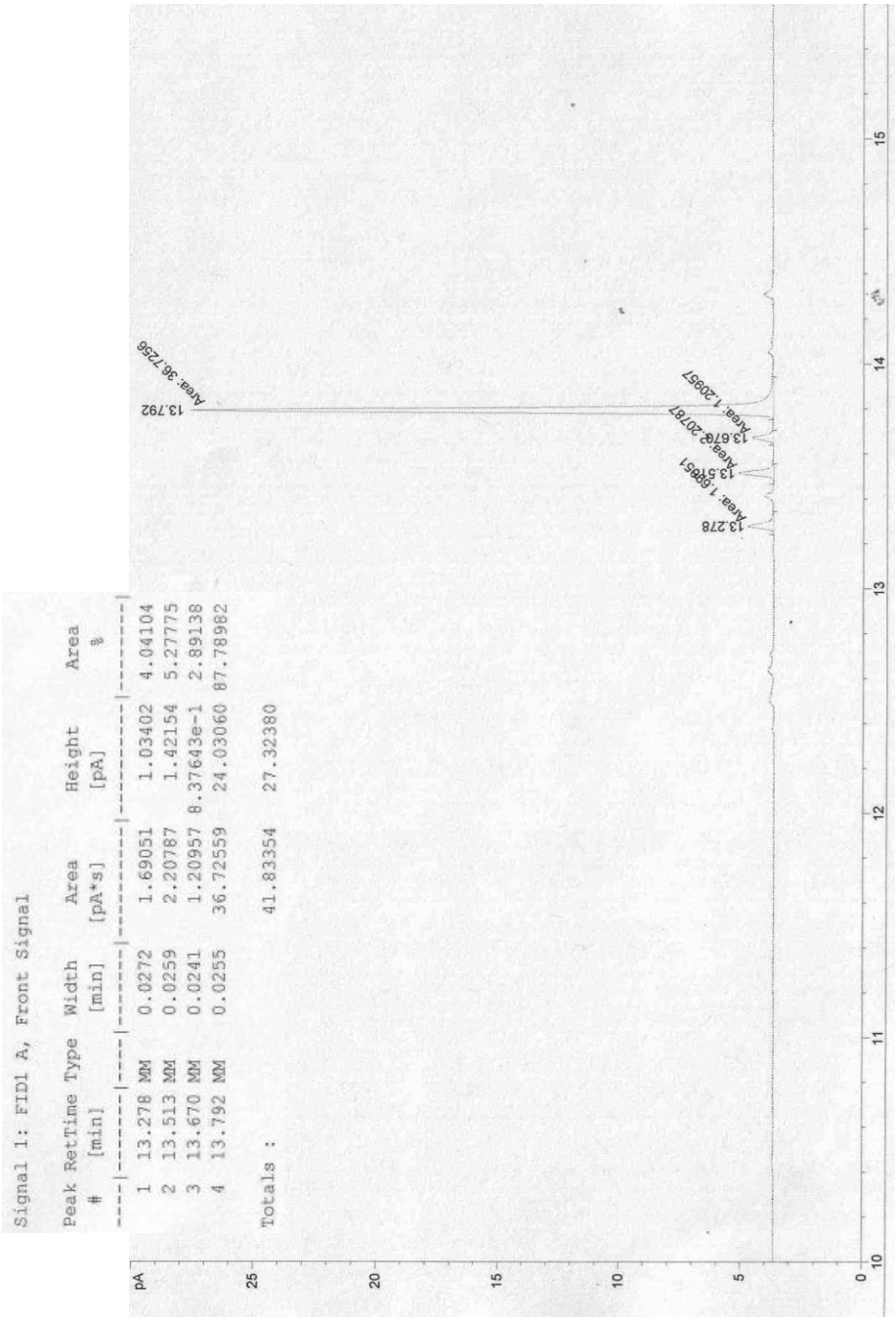


Figure 3.22 Chiral GC data for compound **3.30**

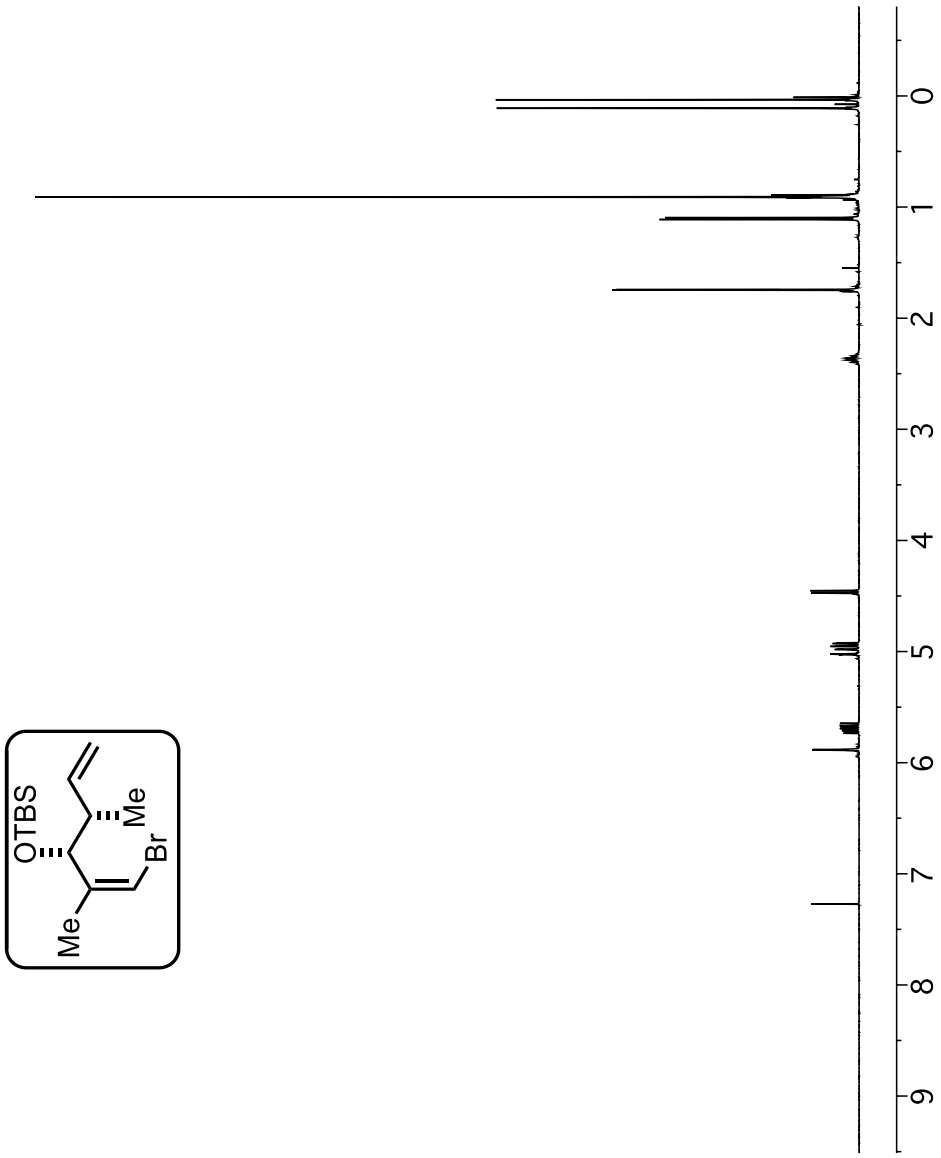


Figure 3.23 ^{1}H NMR spectrum of compound **3.12**

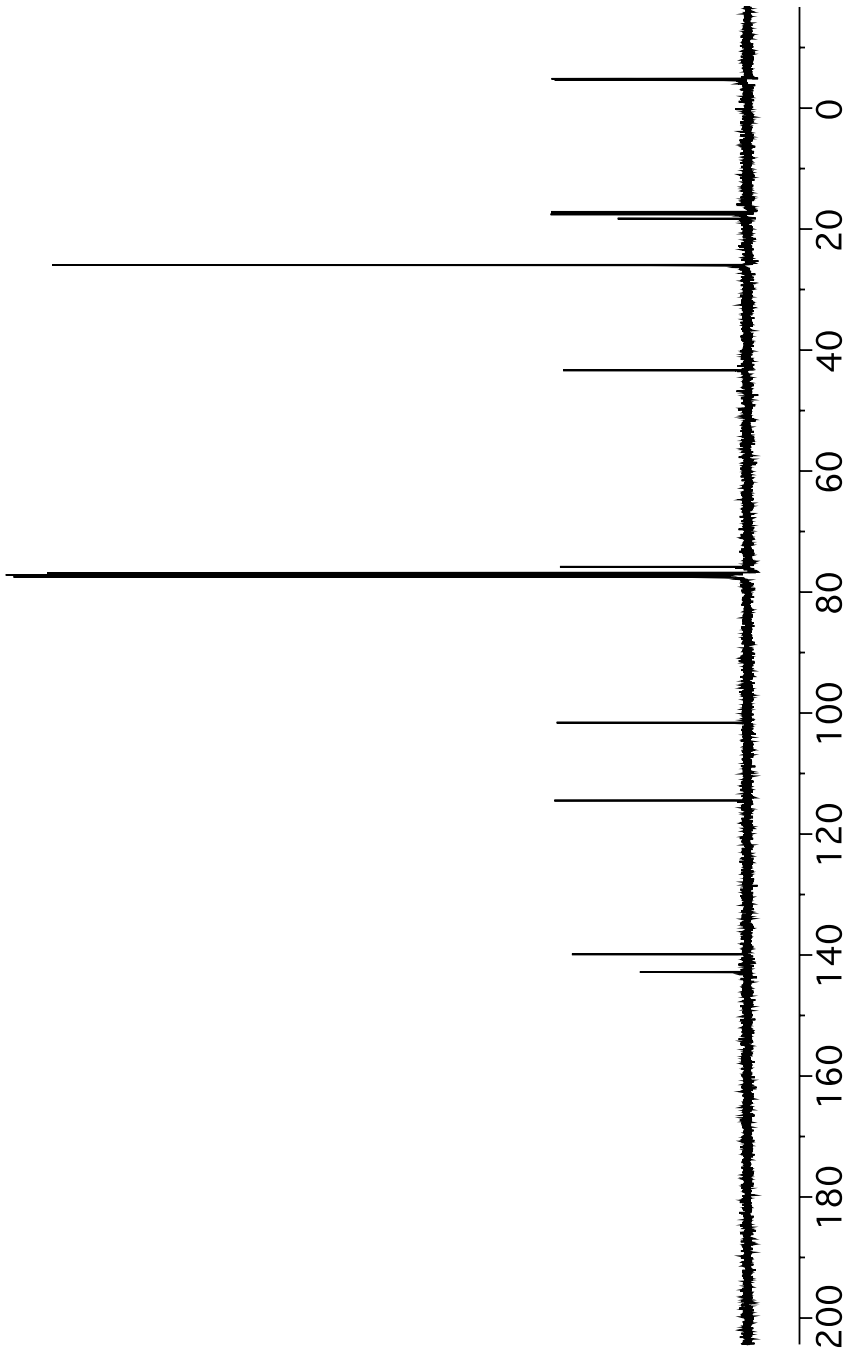


Figure 3.24 ^{13}C NMR spectrum of compound **3.12**

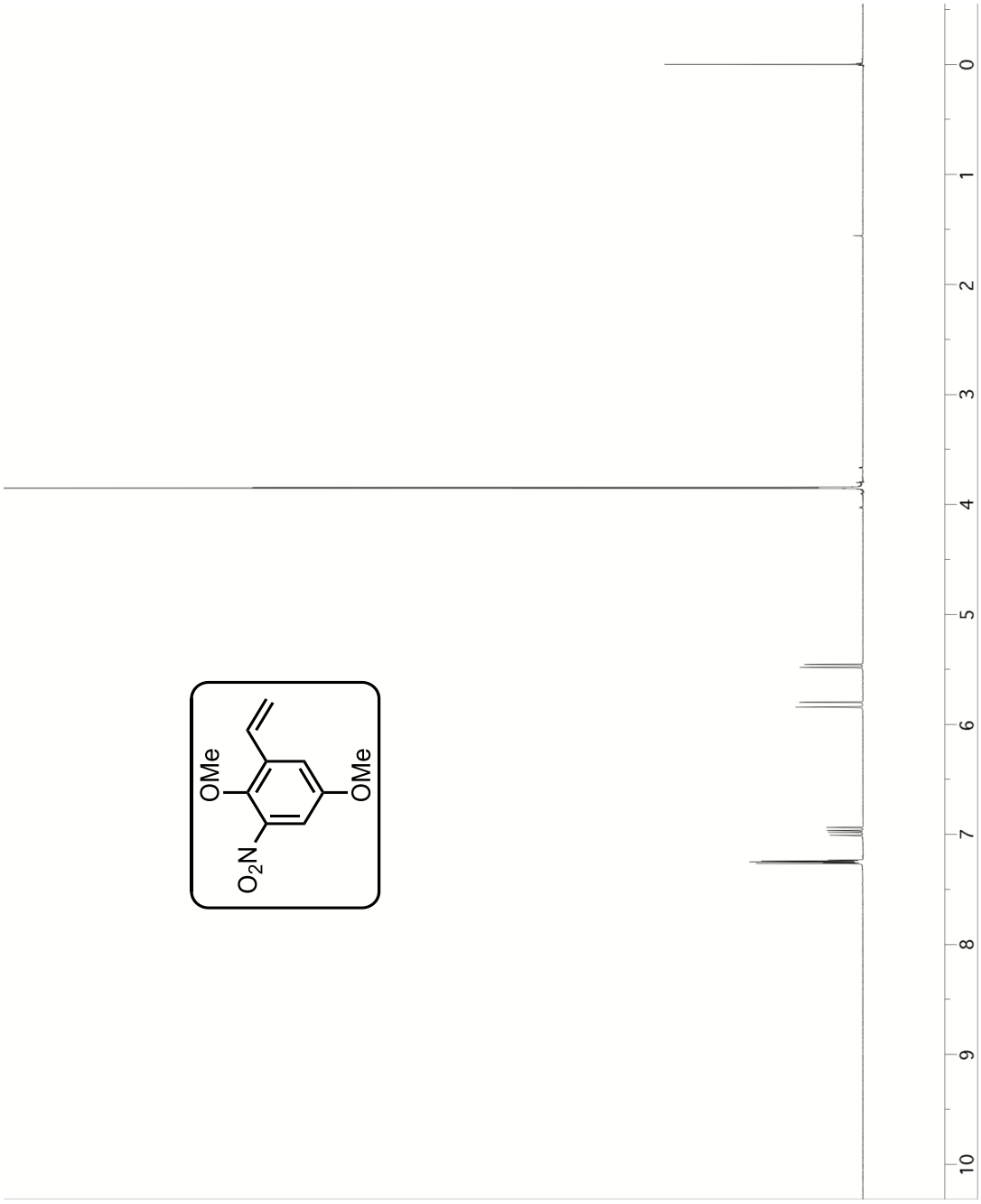


Figure 3.25 ^{1}H NMR spectrum of compound **3.16**

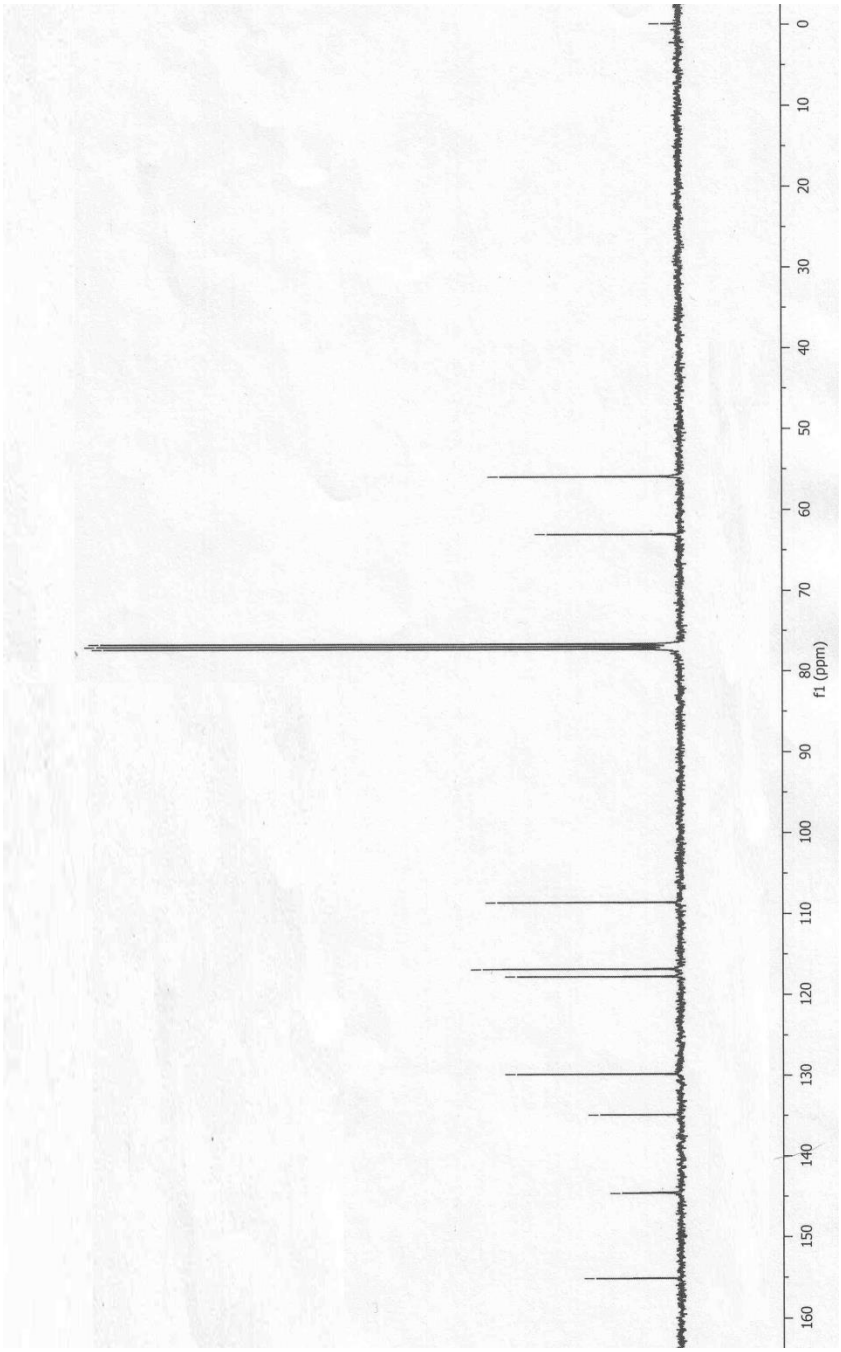


Figure 3.26 ^{13}C NMR spectrum of compound **3.16**

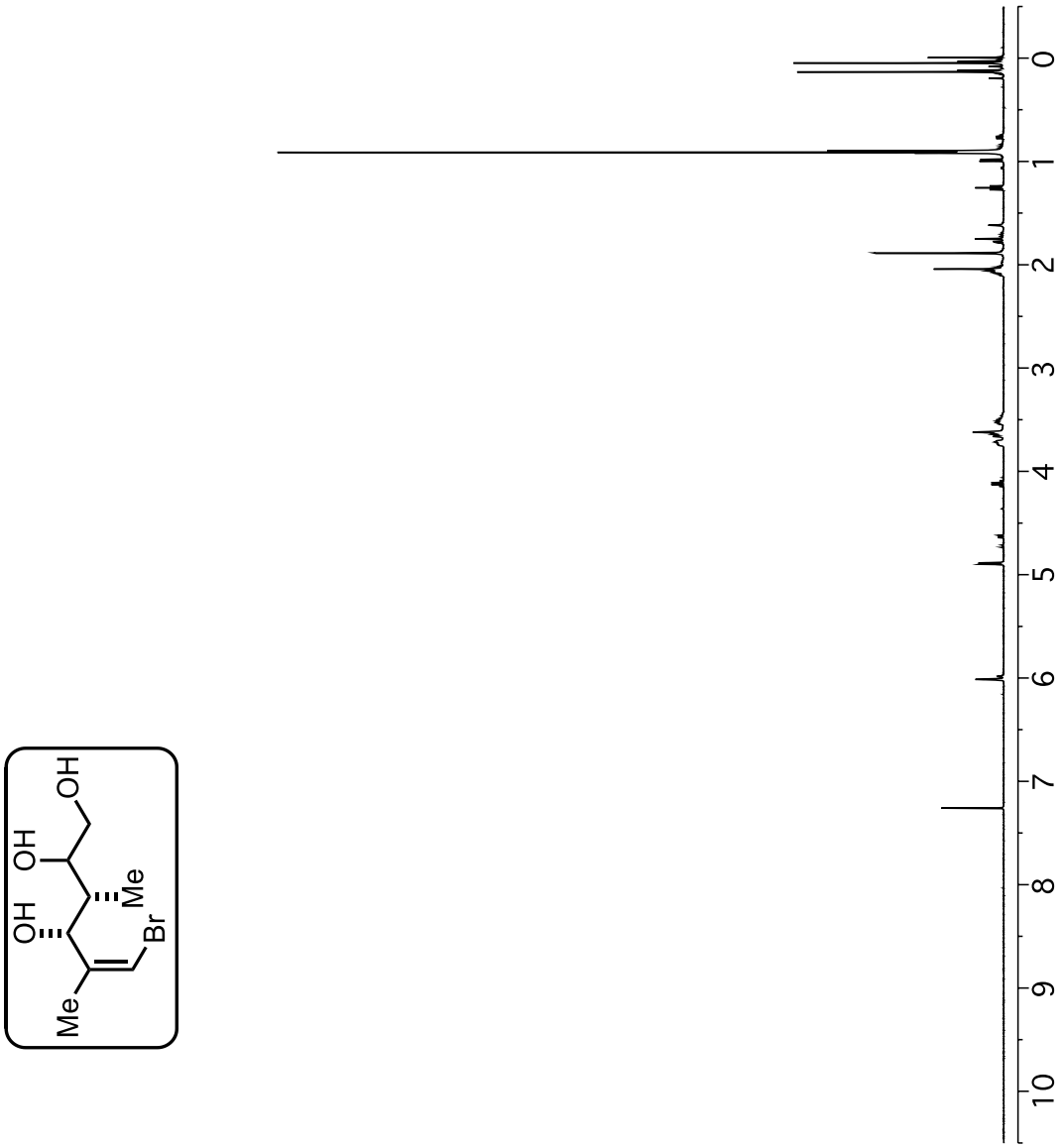


Figure 3.27 ^{1}H NMR spectrum of compound **3.31diol**

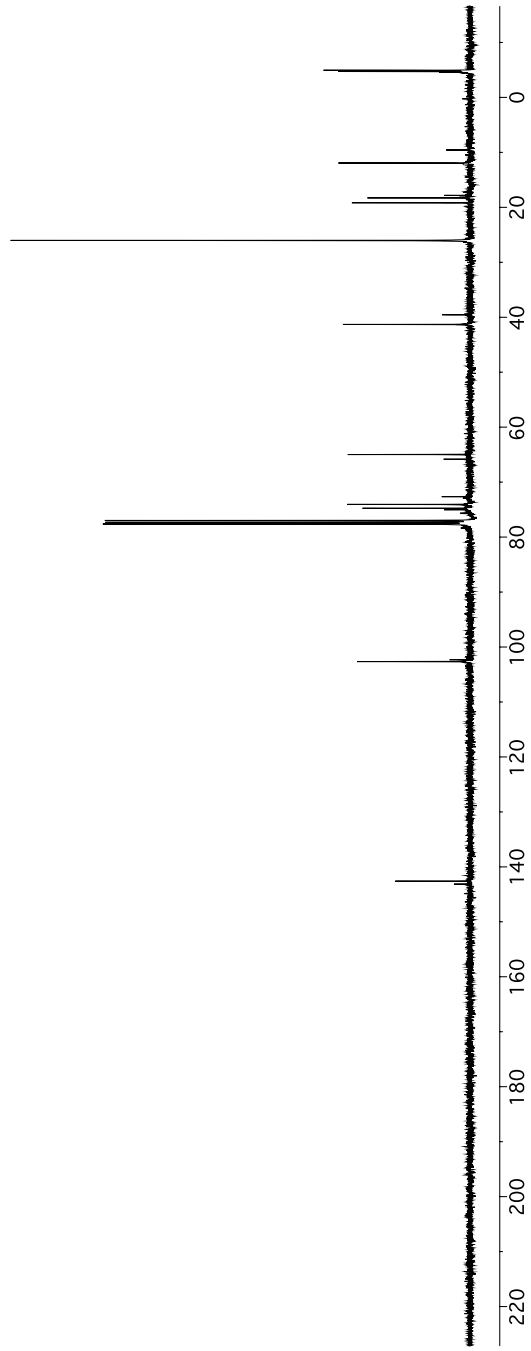


Figure 3.28 ^{13}C NMR spectrum of compound **3.31diol**

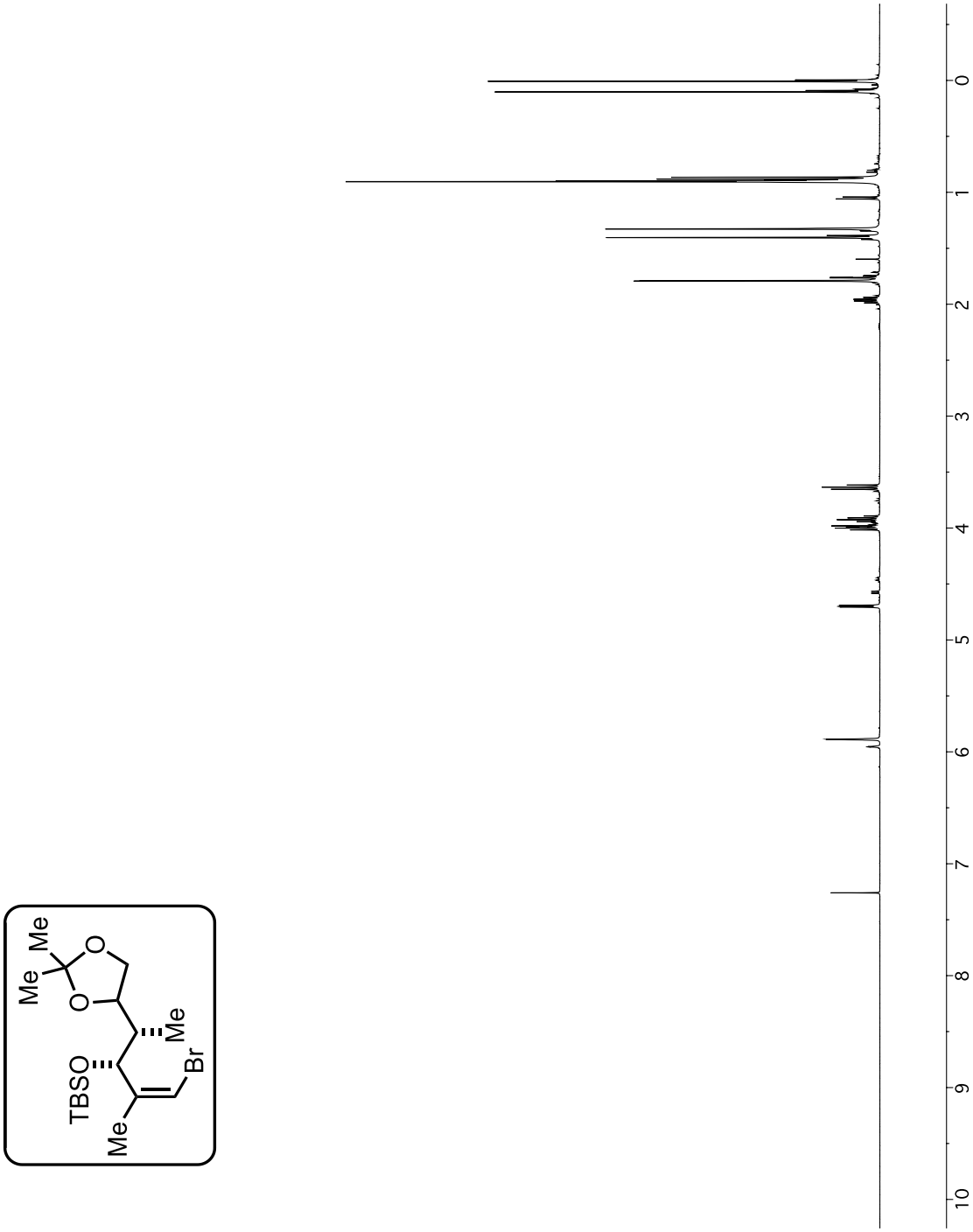


Figure 3.29 ^{1}H NMR spectrum of compound **3.31**

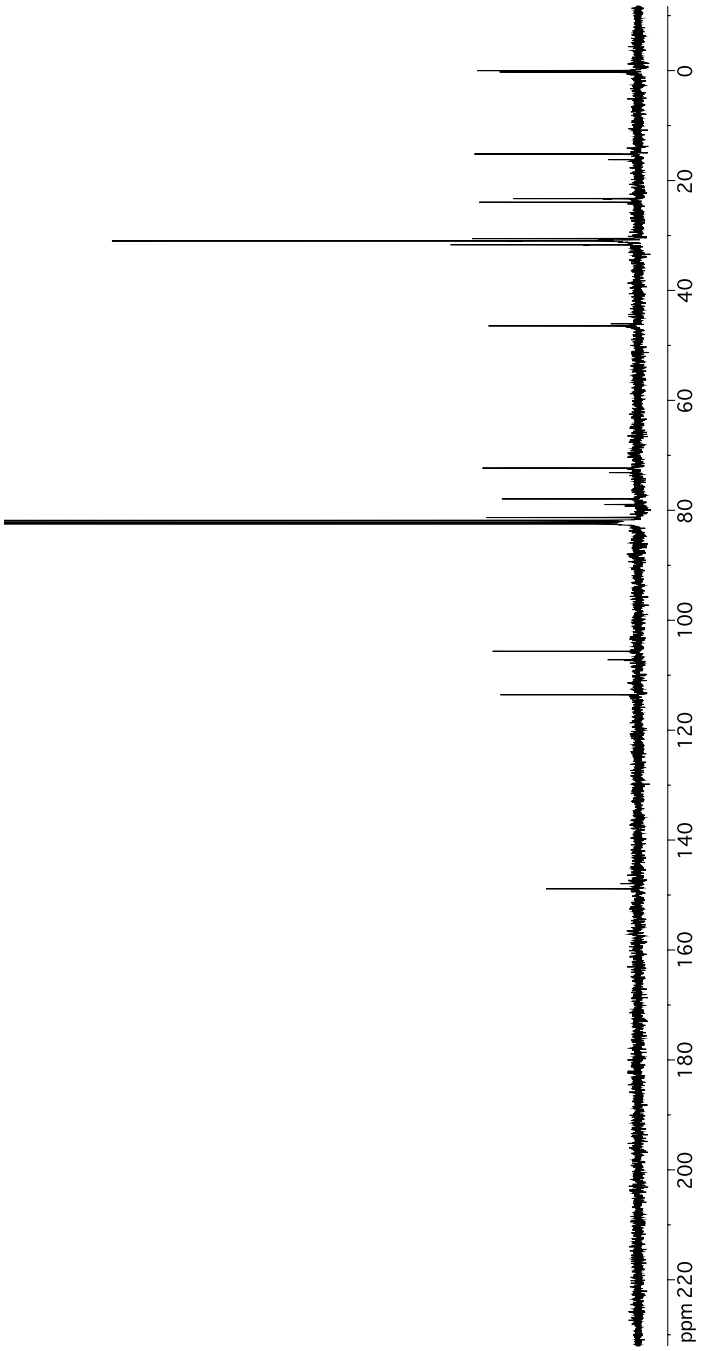


Figure 3.30 ^{13}C NMR spectrum of compound **3.31**

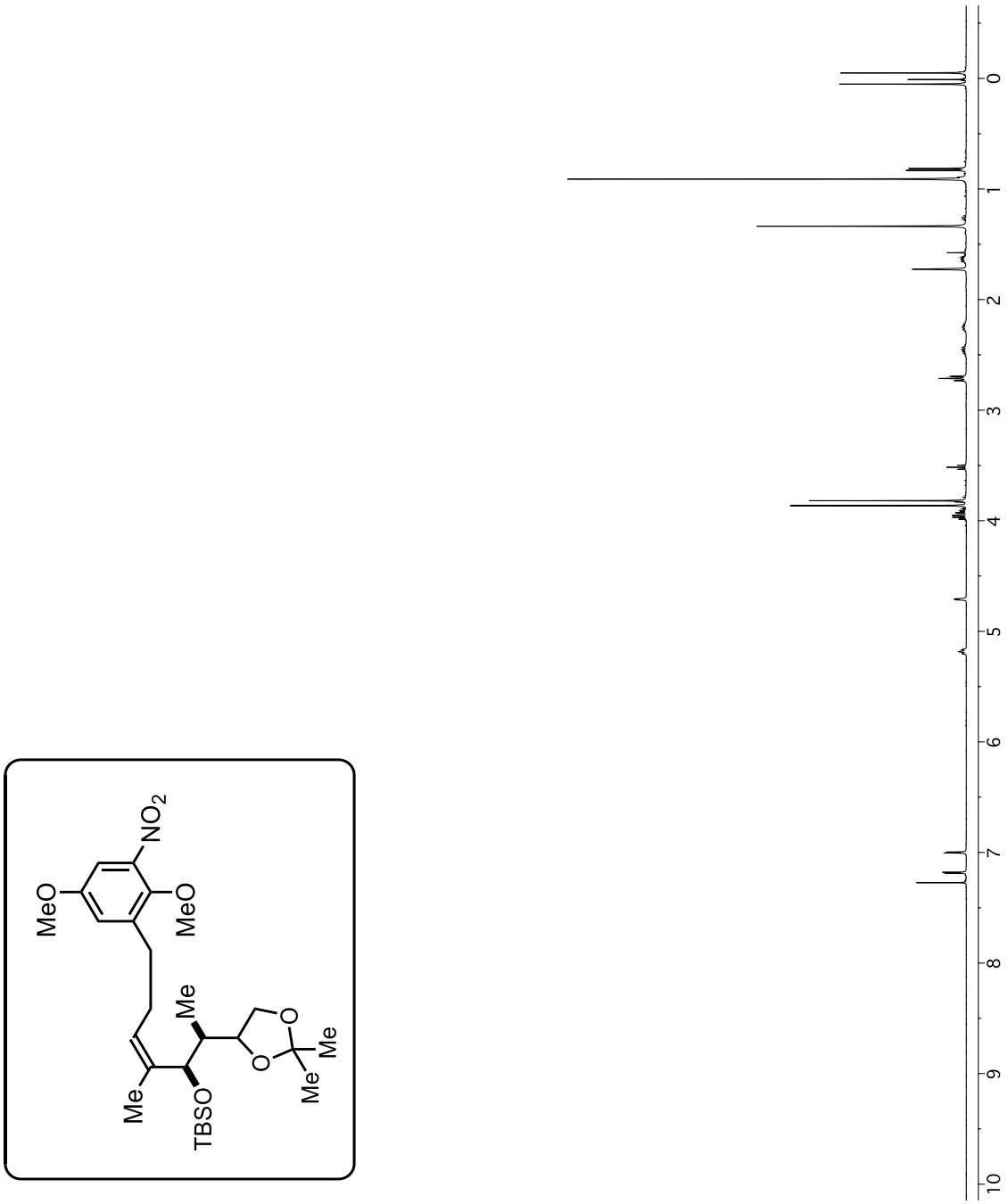


Figure 3.31 ^{1}H NMR spectrum of compound **3.32**

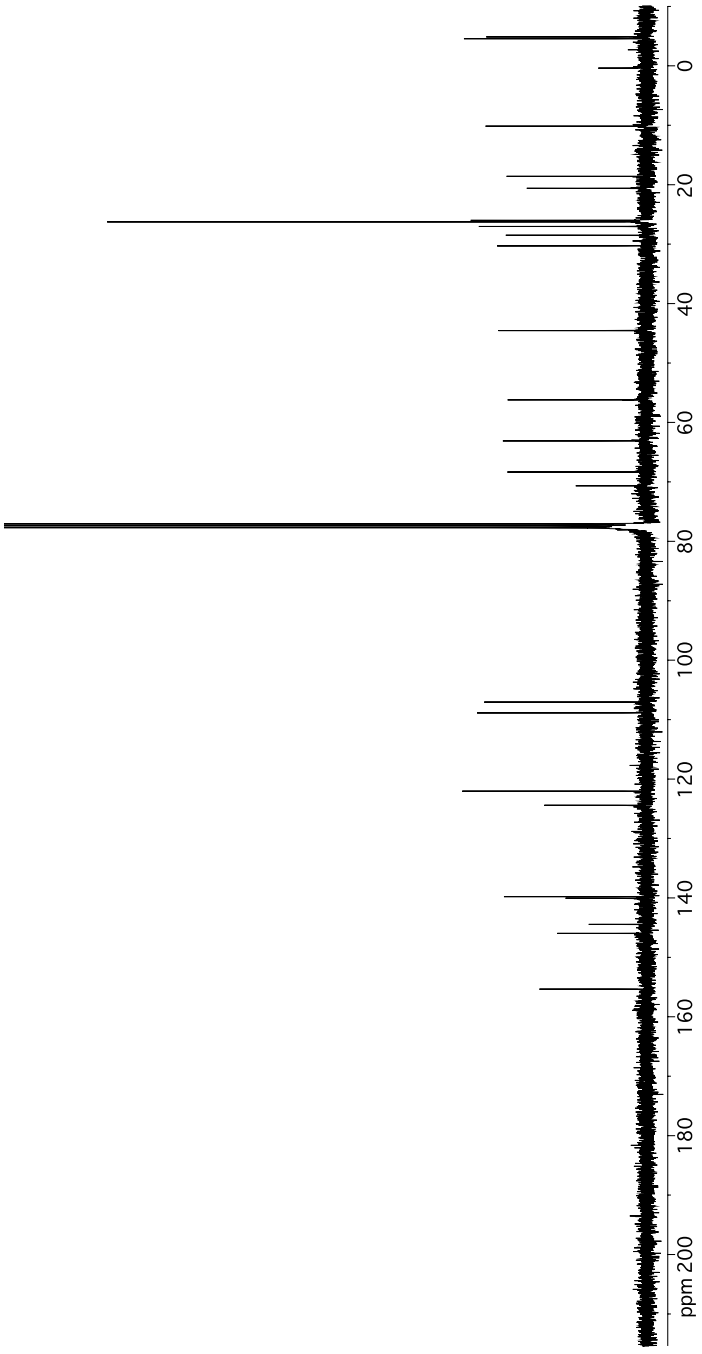


Figure 3.32 ^{13}C NMR spectrum of compound **3.32**

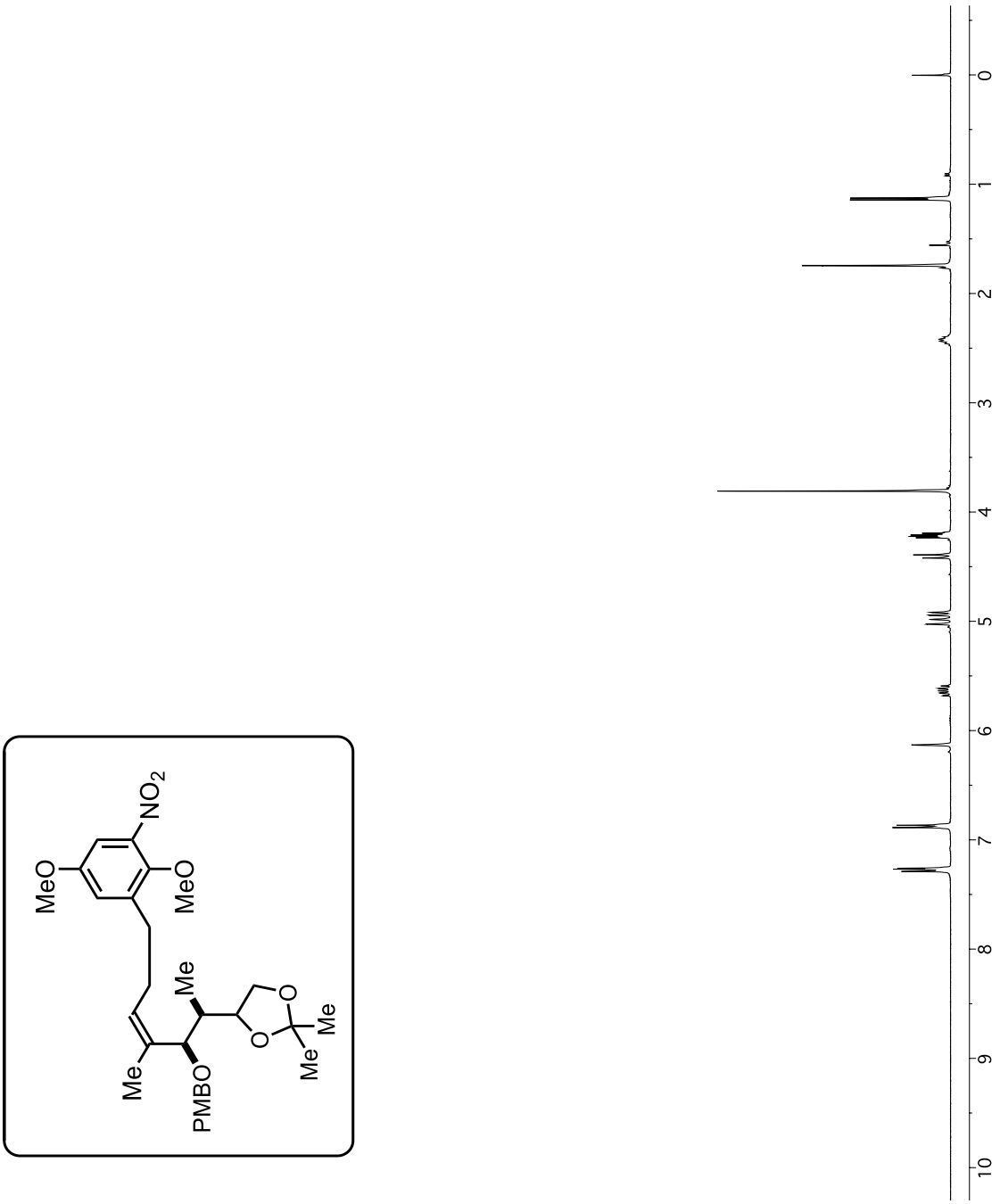


Figure 3.33 ^{1}H NMR spectrum of compound **3.34**

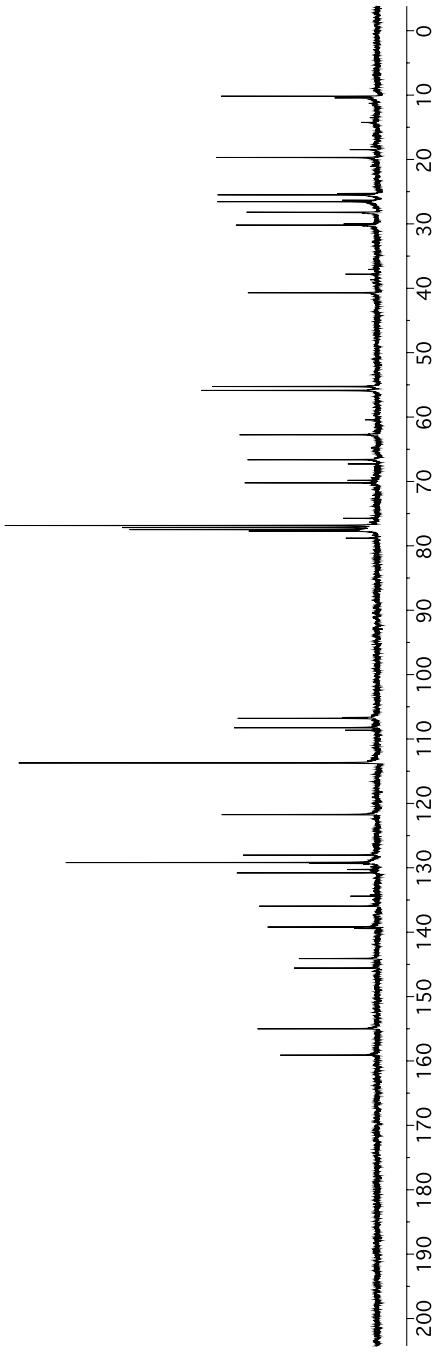


Figure 3.34 ^{13}C NMR spectrum of compound **3.34**

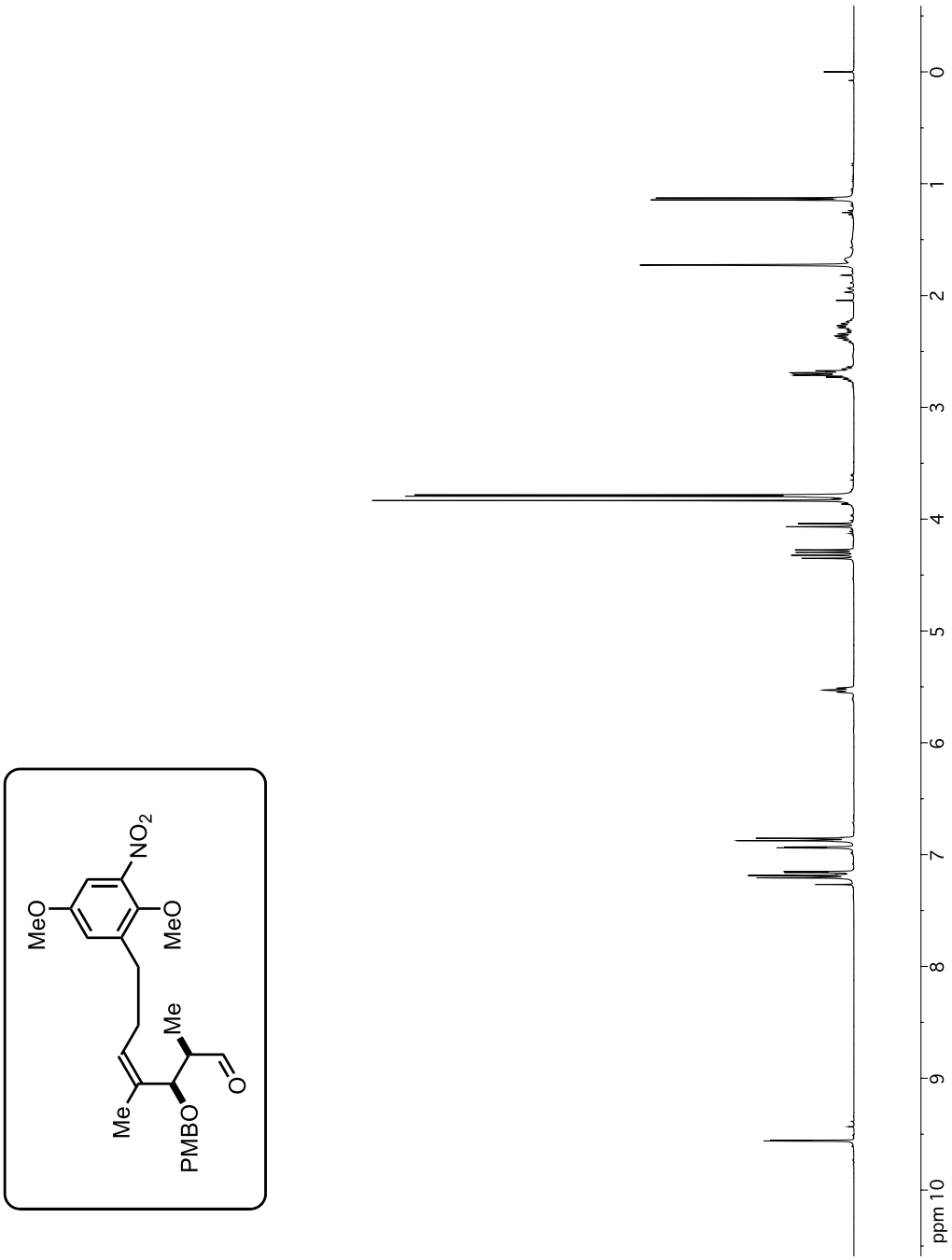


Figure 3.35 ^{1}H NMR spectrum of compound **3.35**

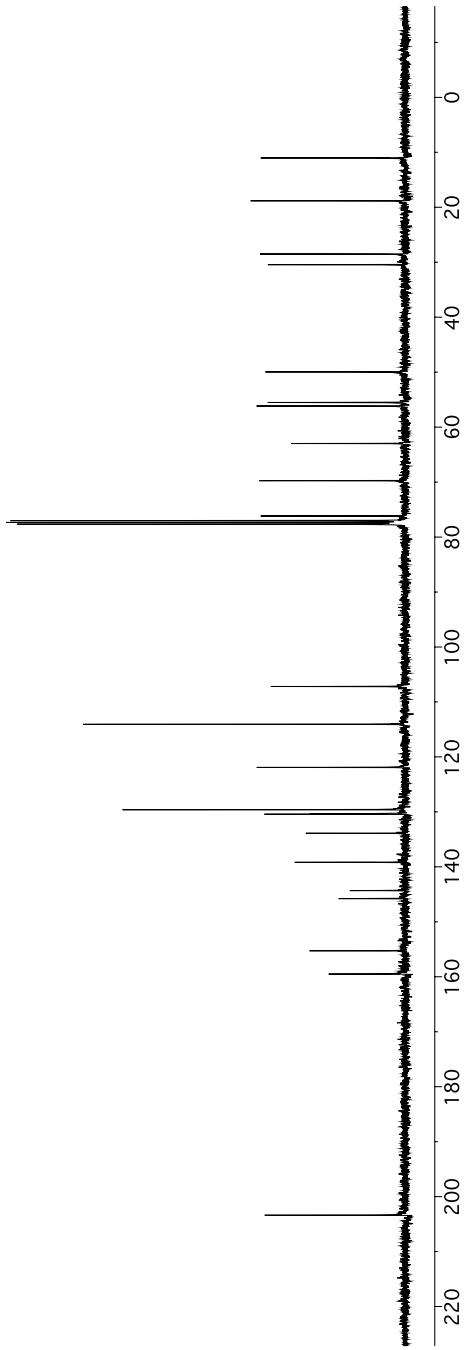


Figure 3.36 ^{13}C NMR spectrum of compound **3.35**

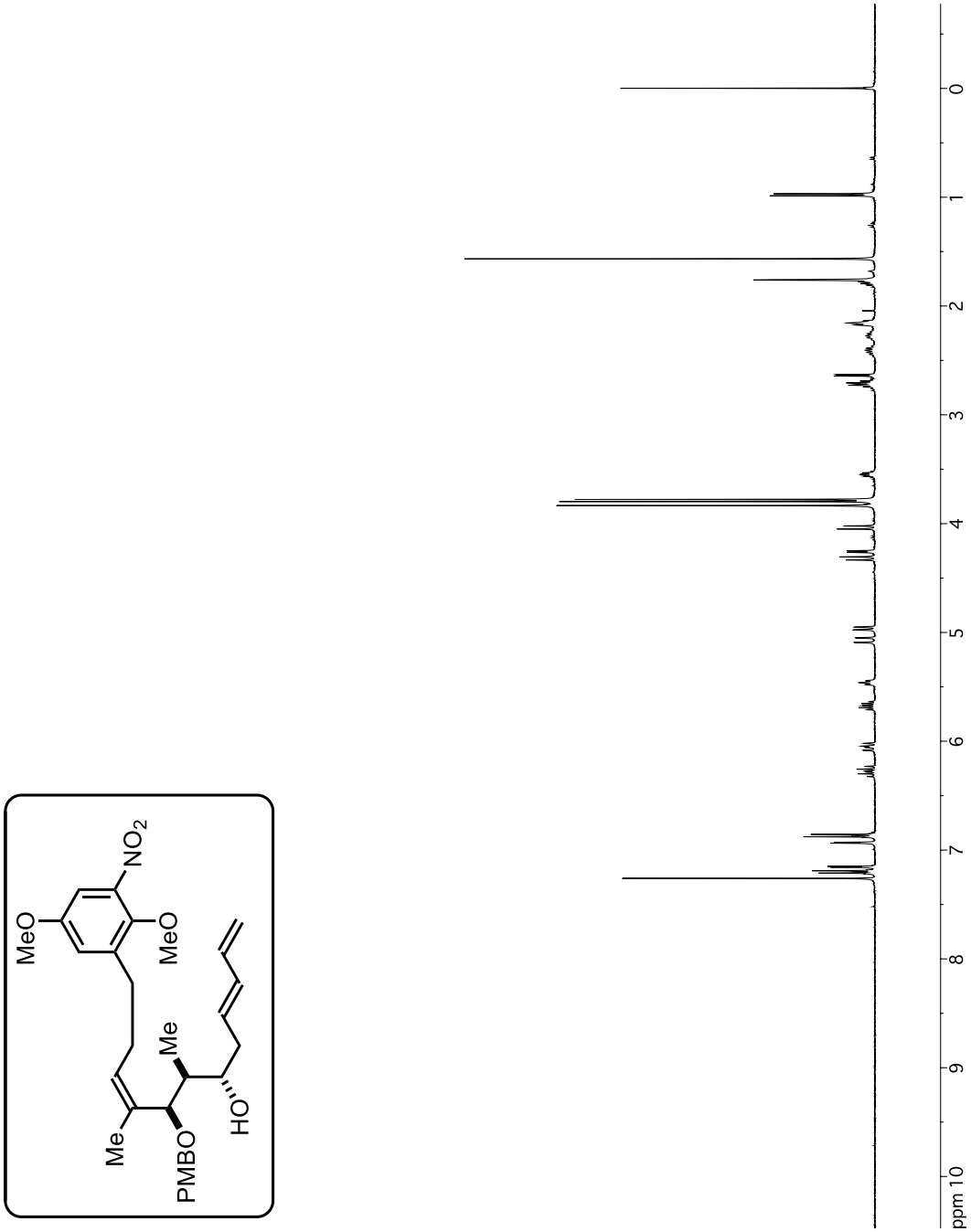


Figure 3.37 ^{1}H NMR spectrum of compound **3.36**

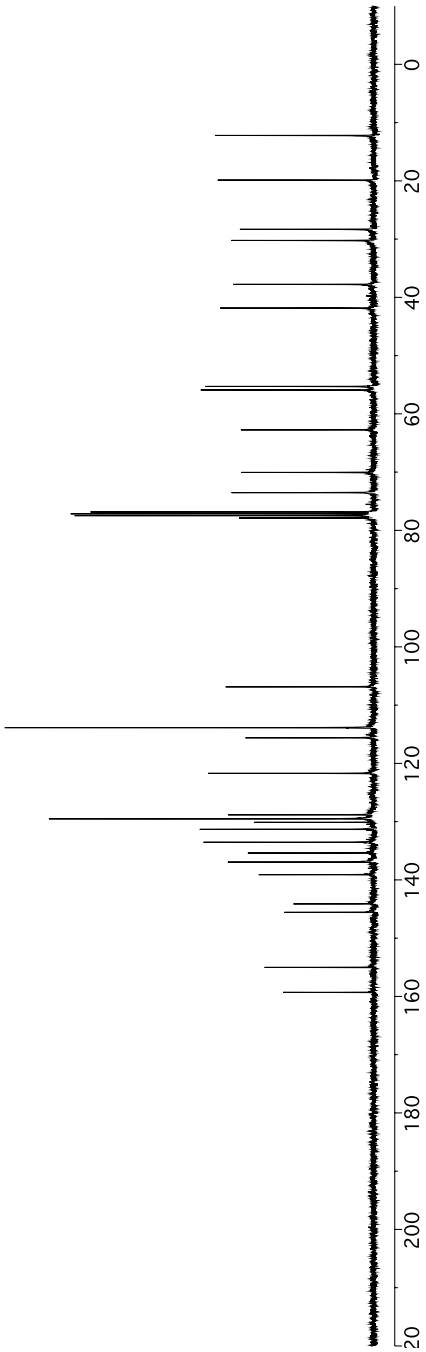
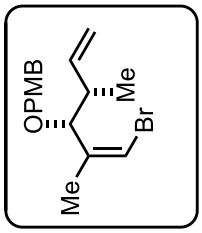


Figure 3.38 ^{13}C NMR spectrum of compound **3.36**



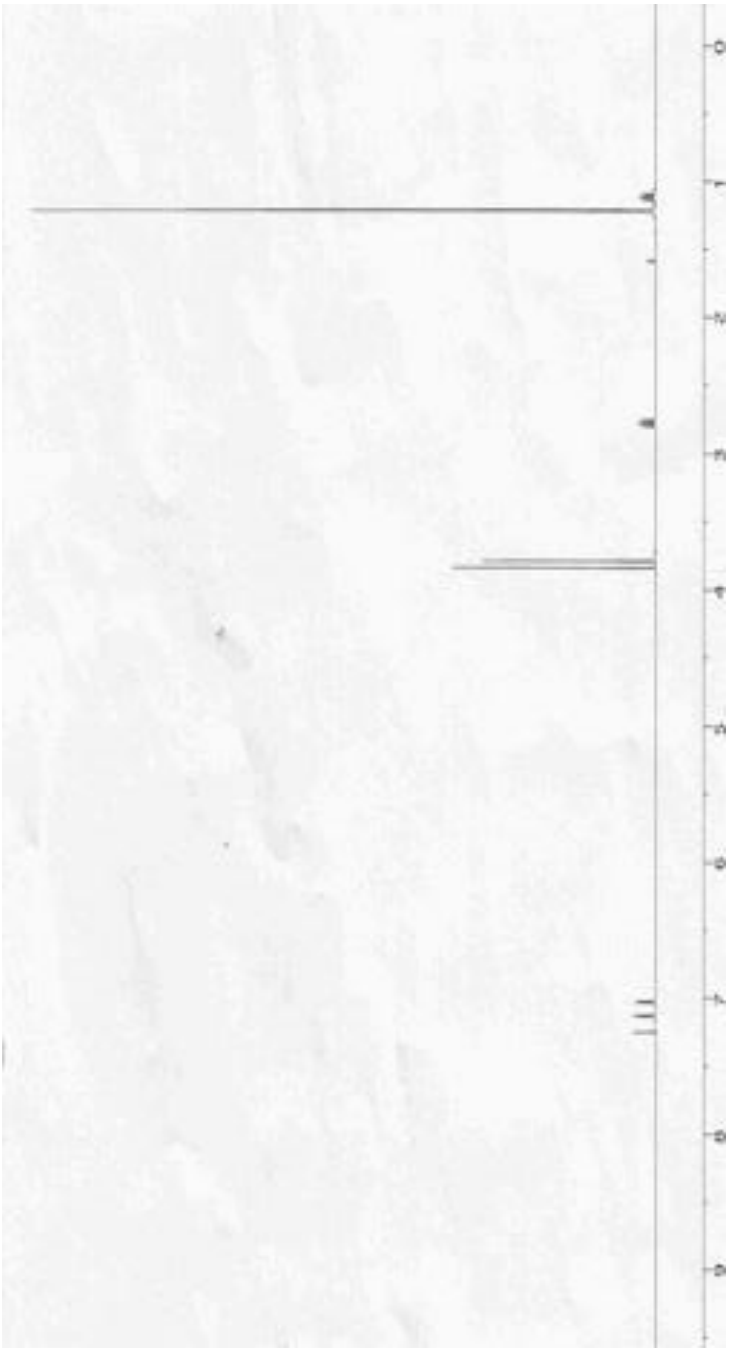


Figure 3.39 ^{1}H NMR spectrum of compound **3.37**

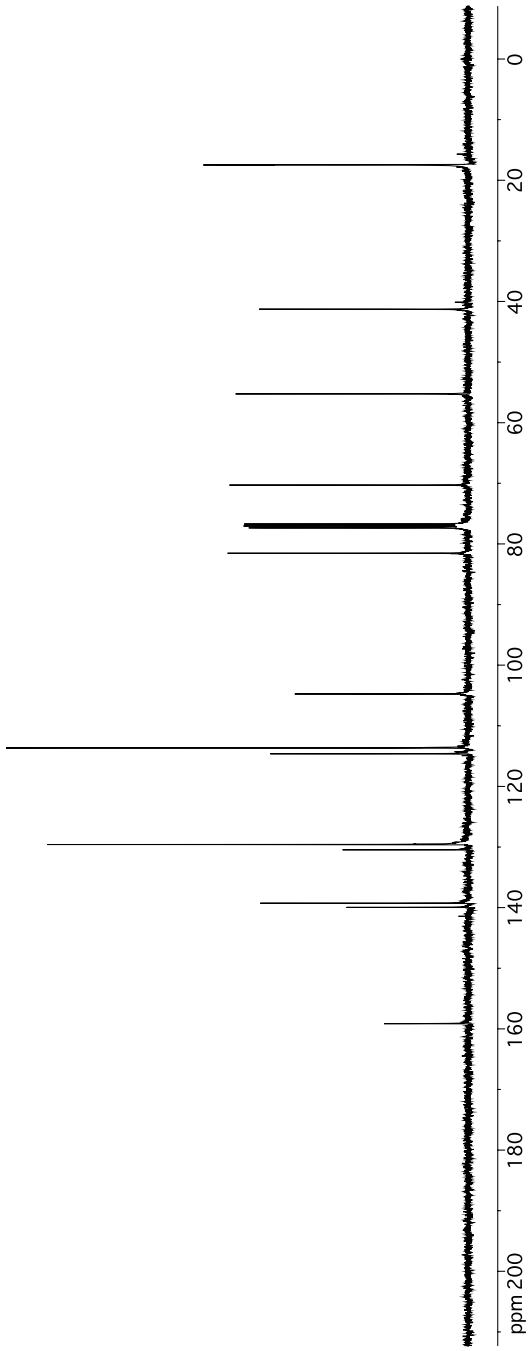


Figure 3.40 ^{13}C NMR spectrum of compound **3.37**

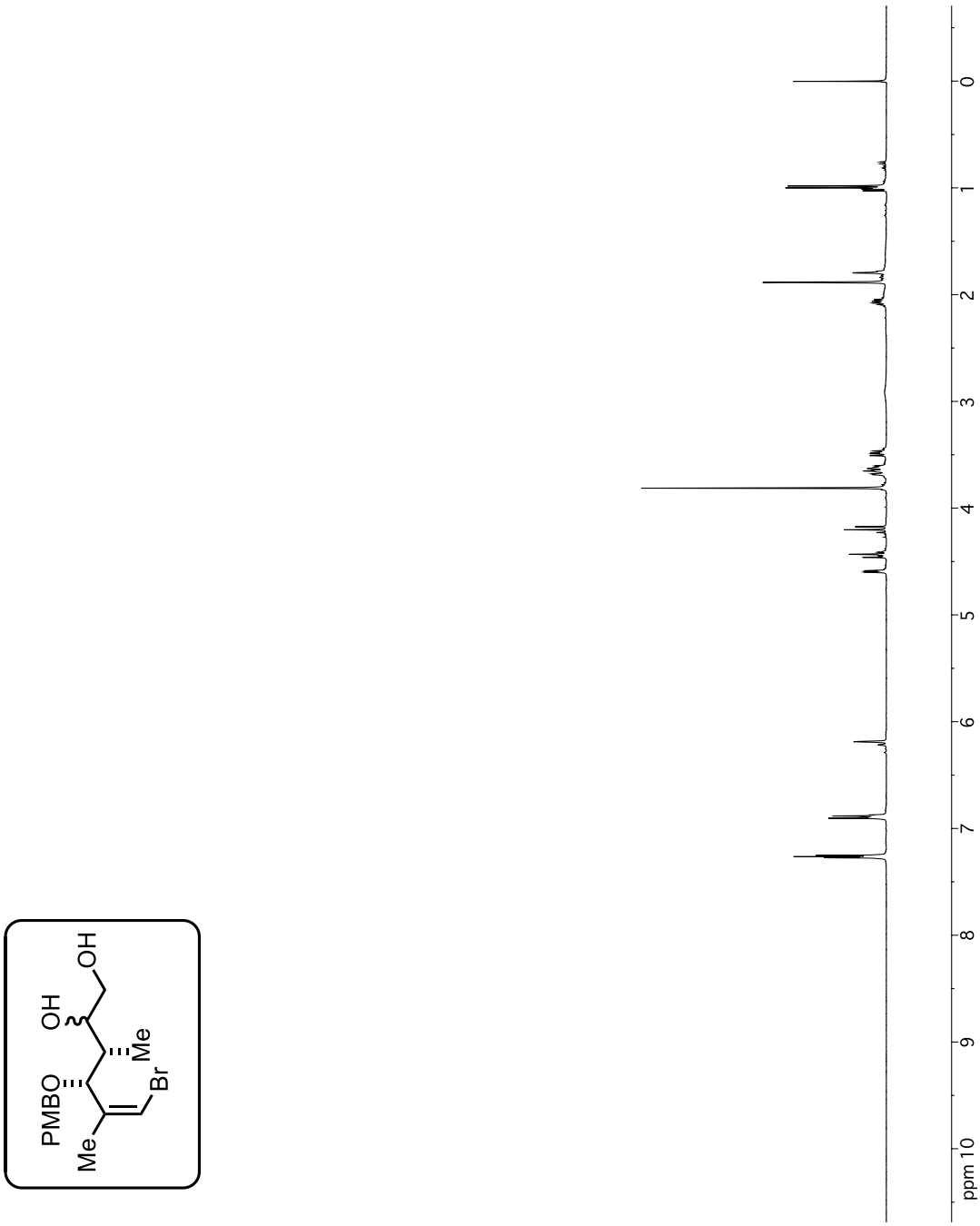


Figure 3.41 ^{1}H NMR spectrum of compound **3.38**

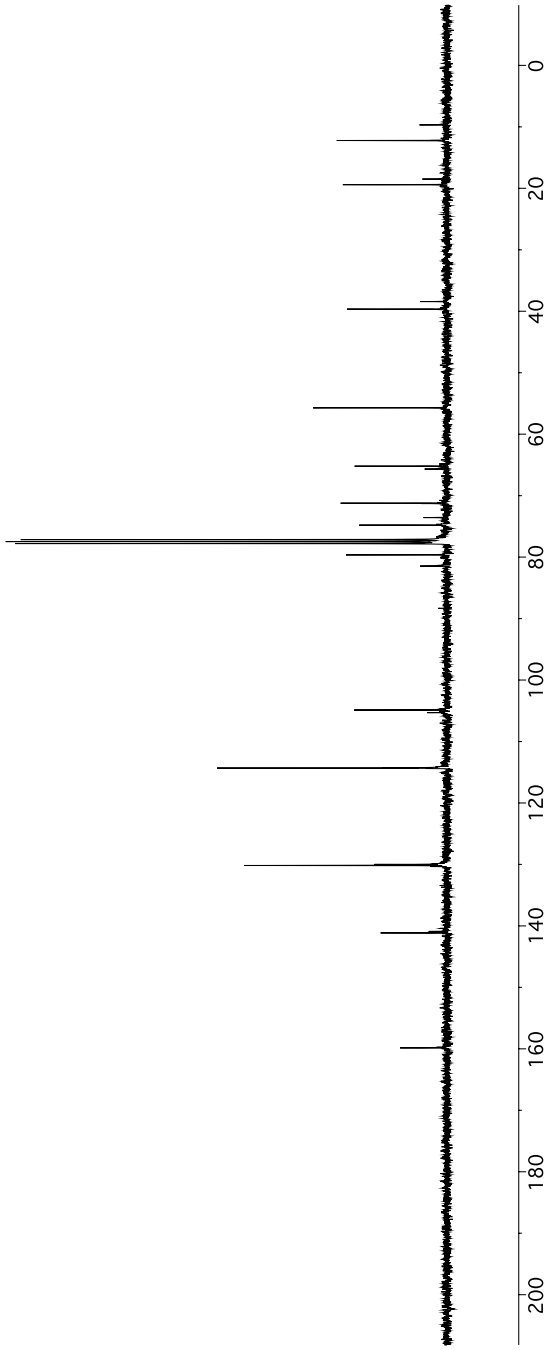


Figure 3.42 ^{13}C NMR spectrum of compound **3.38**

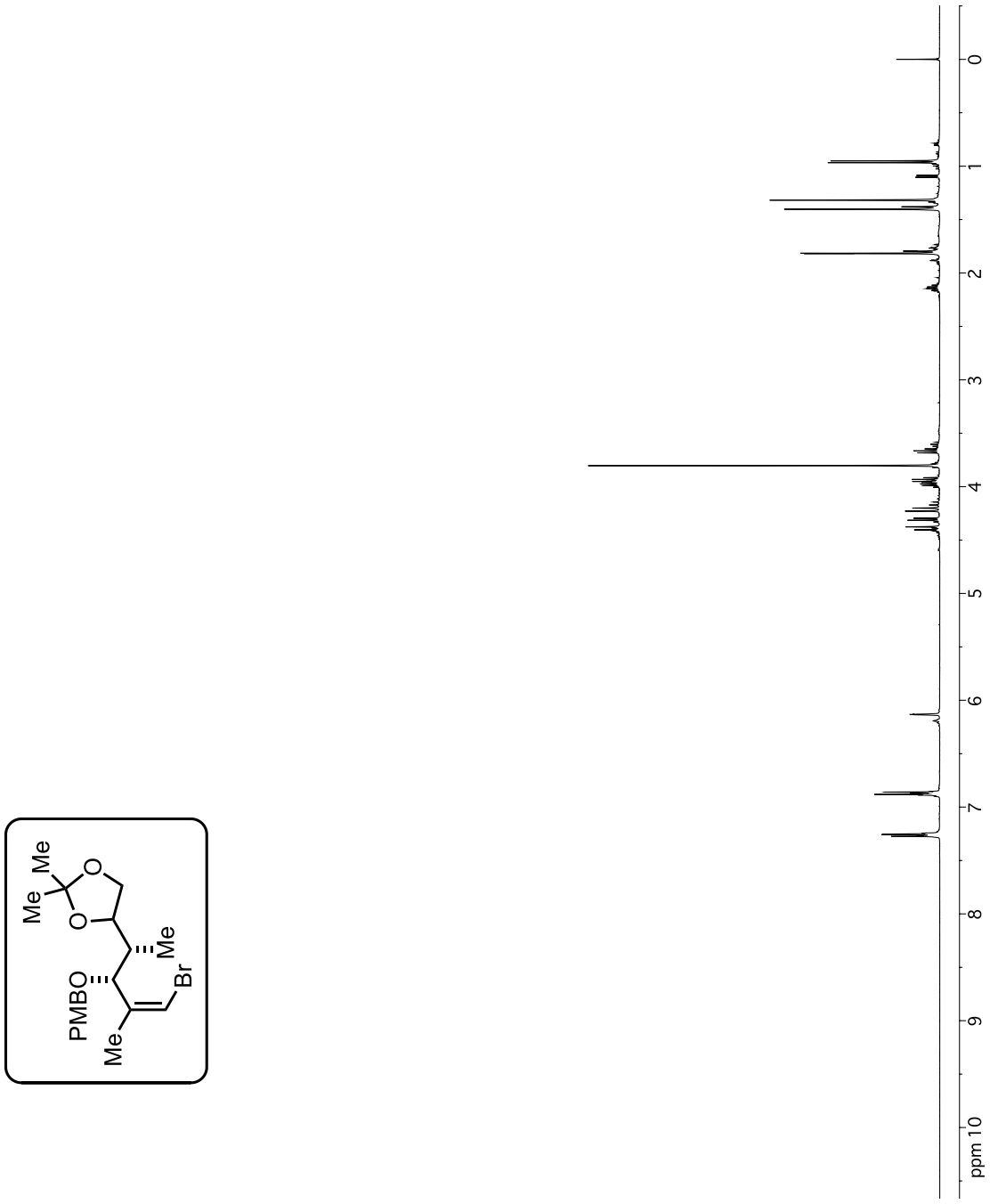


Figure 3.43 ^{1}H NMR spectrum of compound **3.39**

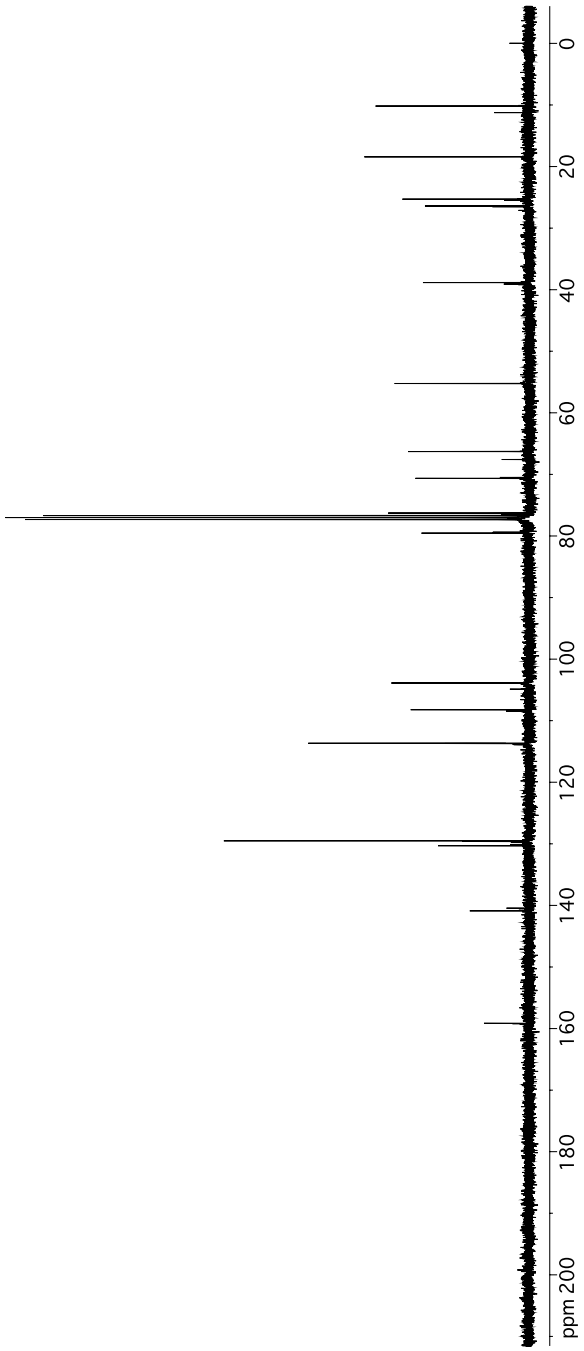


Figure 3.44 ^{13}C NMR spectrum of compound **3.39**

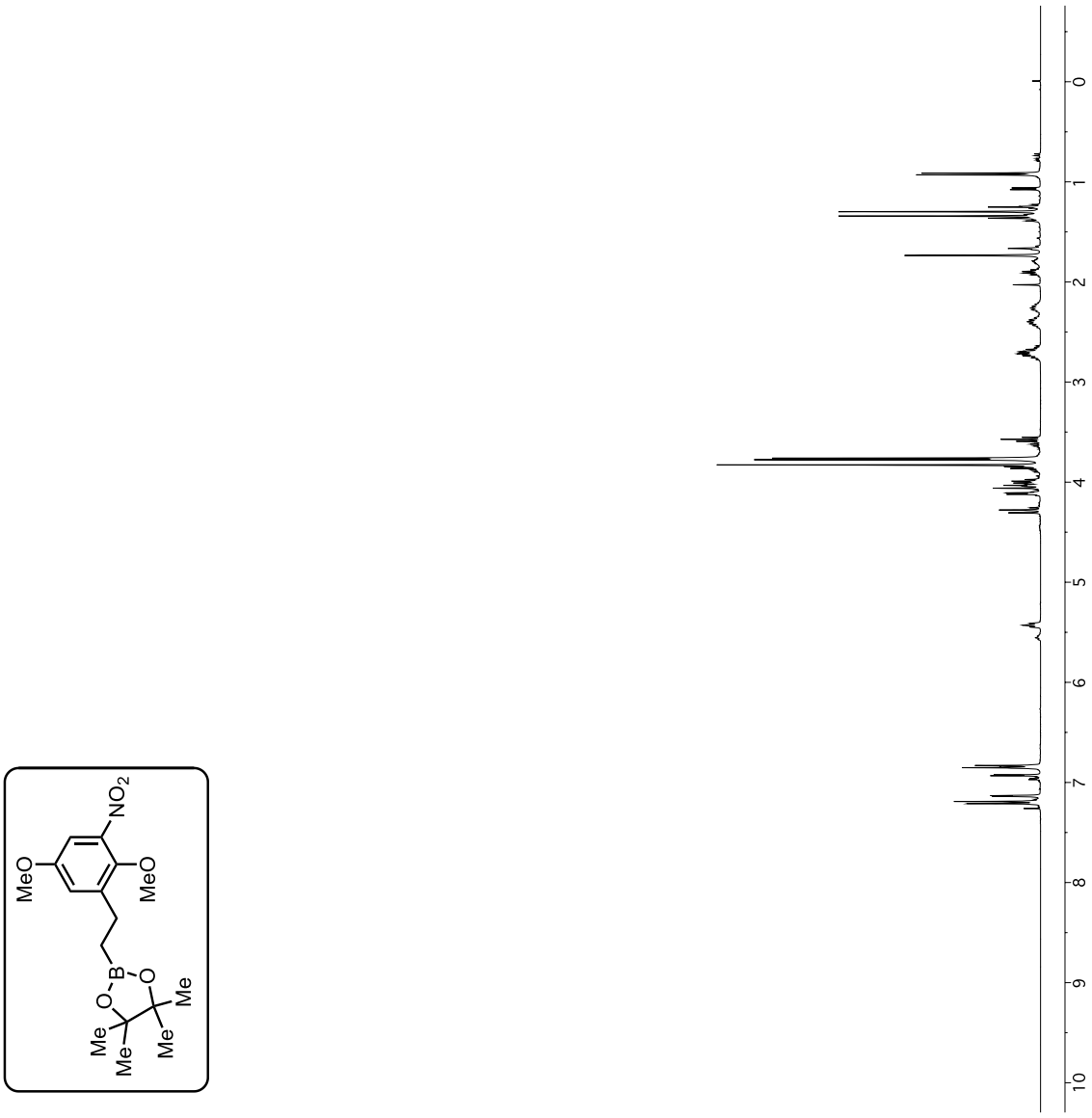


Figure 3.45 ^{1}H NMR spectrum of compound **3.40**

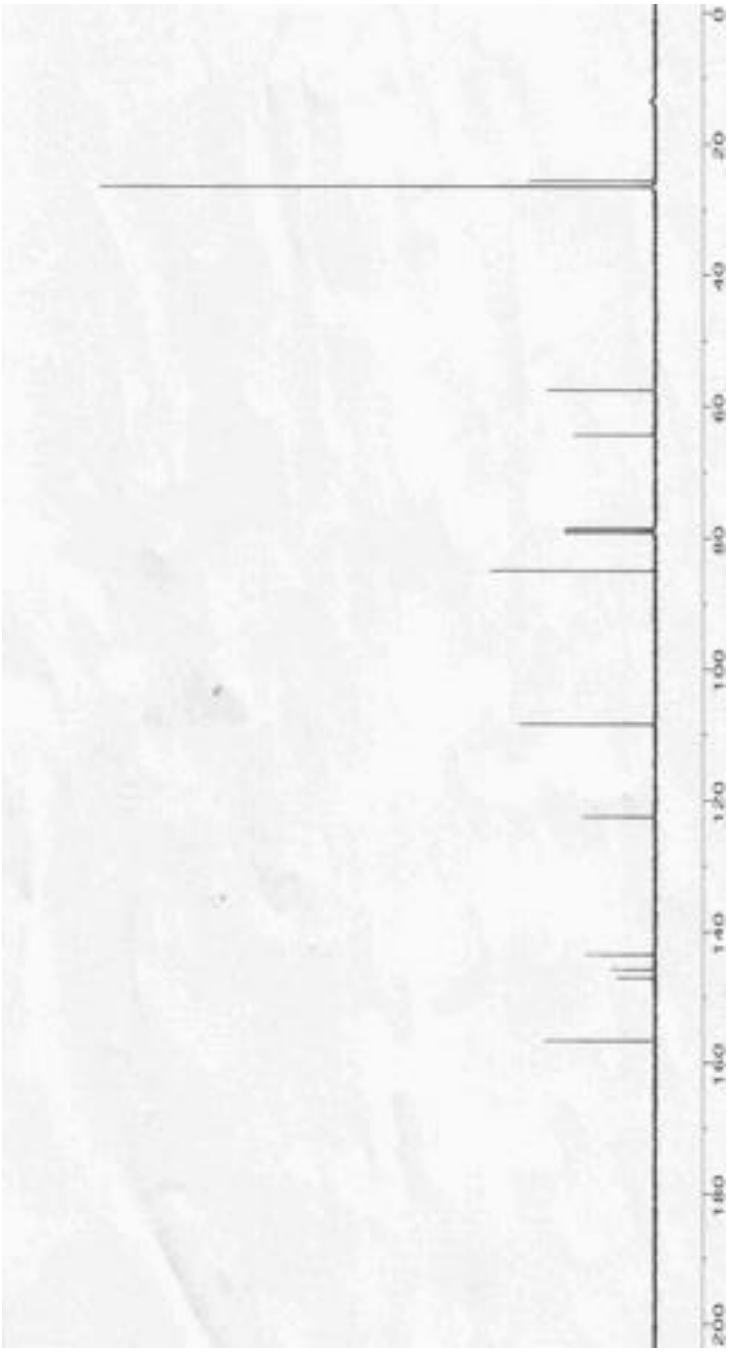


Figure 3.46 ^{13}C NMR spectrum of compound **3.40**

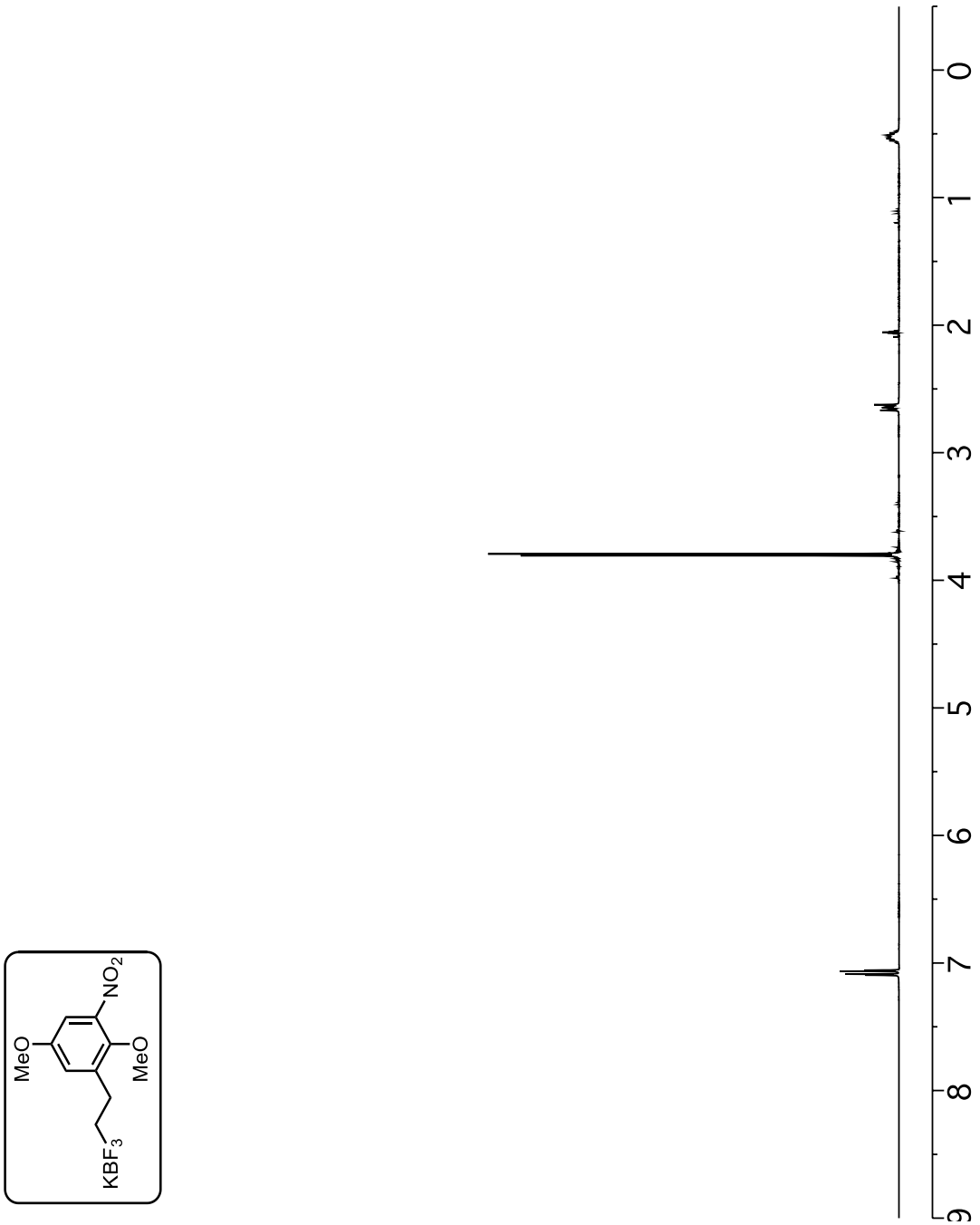


Figure 3.47 ^{1}H NMR spectrum of compound **3.41**

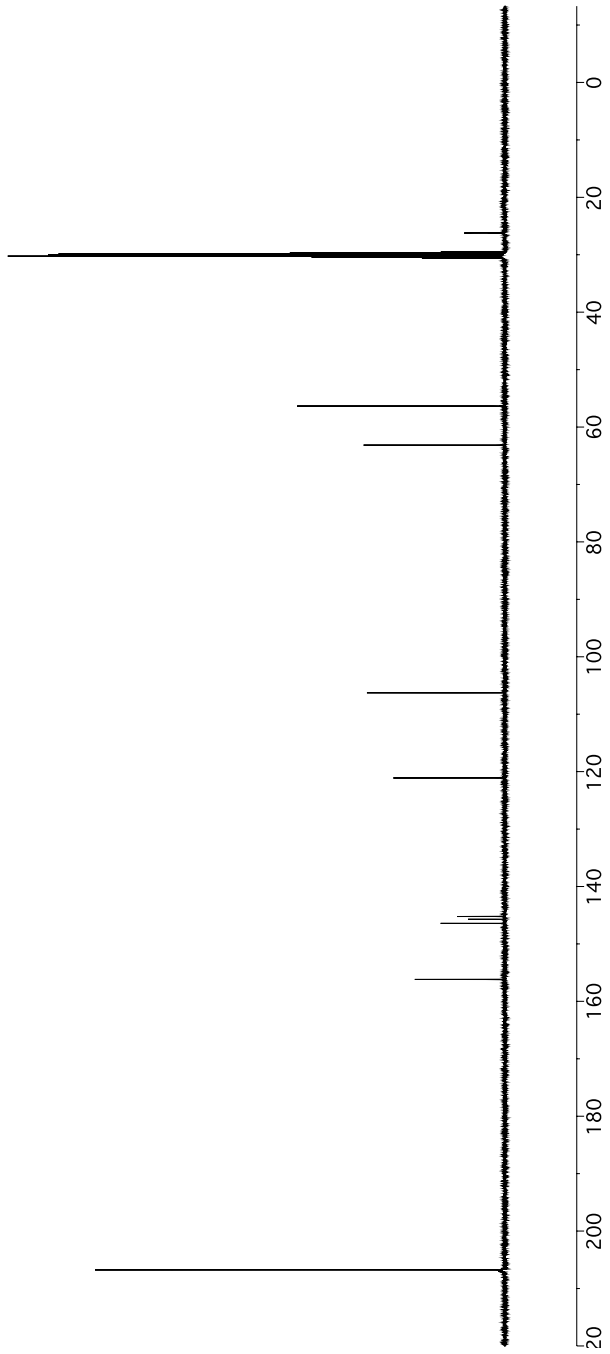


Figure 3.48 ^{13}C NMR spectrum of compound **3.41**

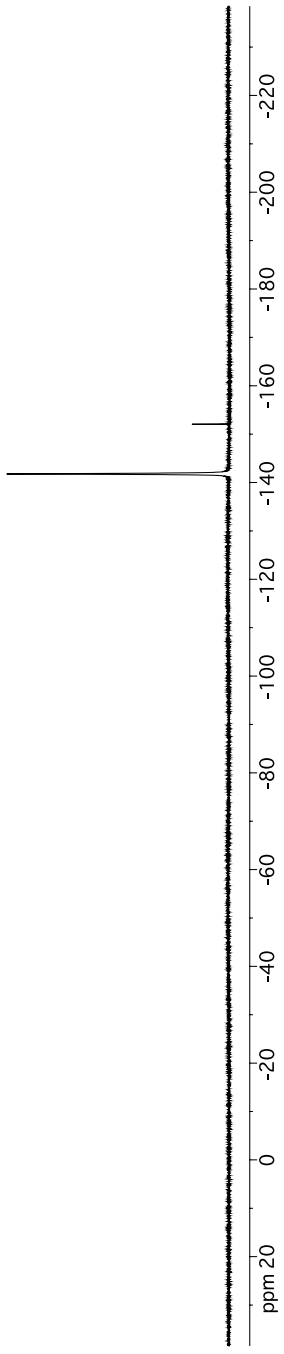


Figure 3.49 ^{19}F NMR spectrum of compound **3.41**

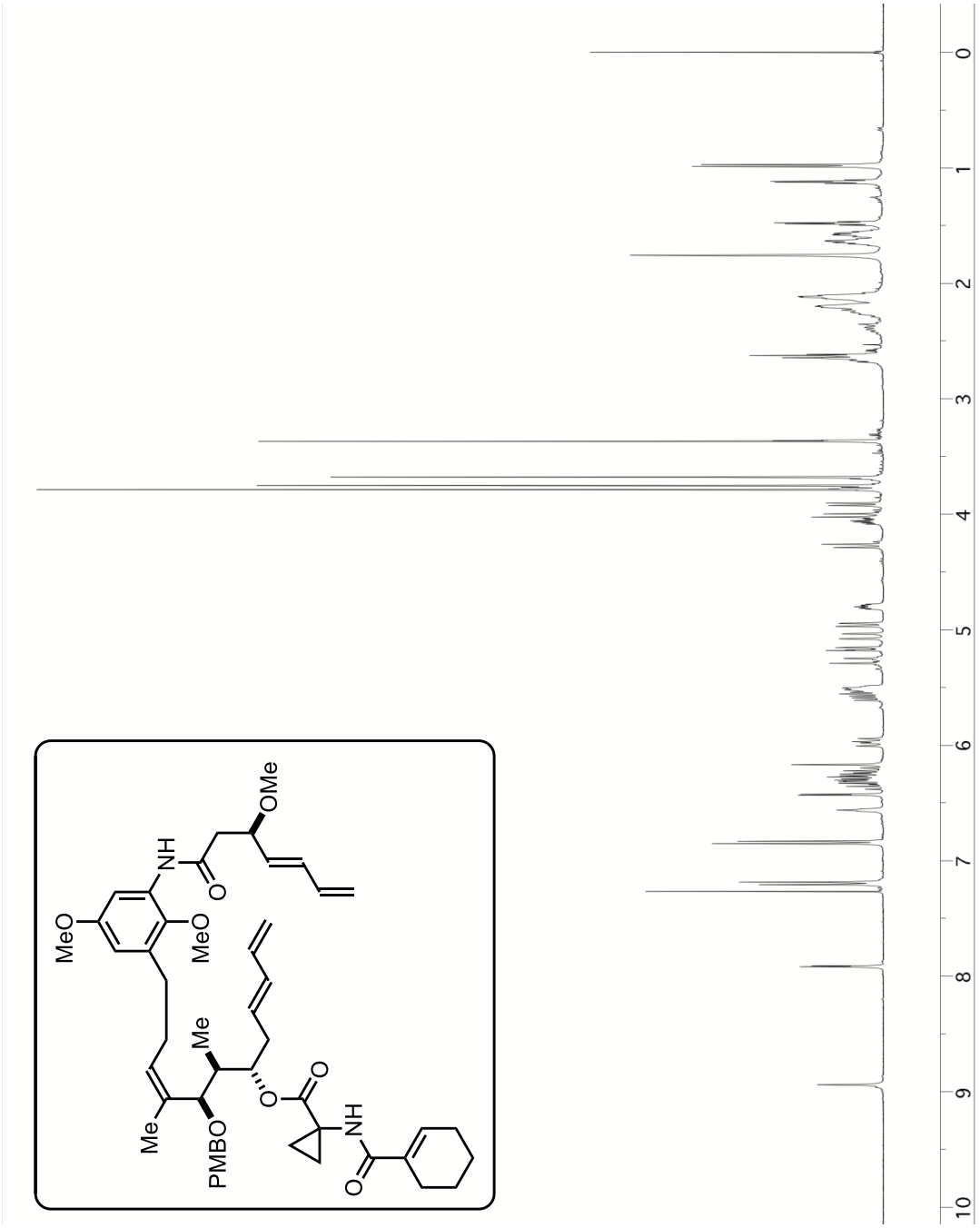


Figure 3.50 ^{1}H NMR spectrum of cytotrienin A bis(diene) **3.55**

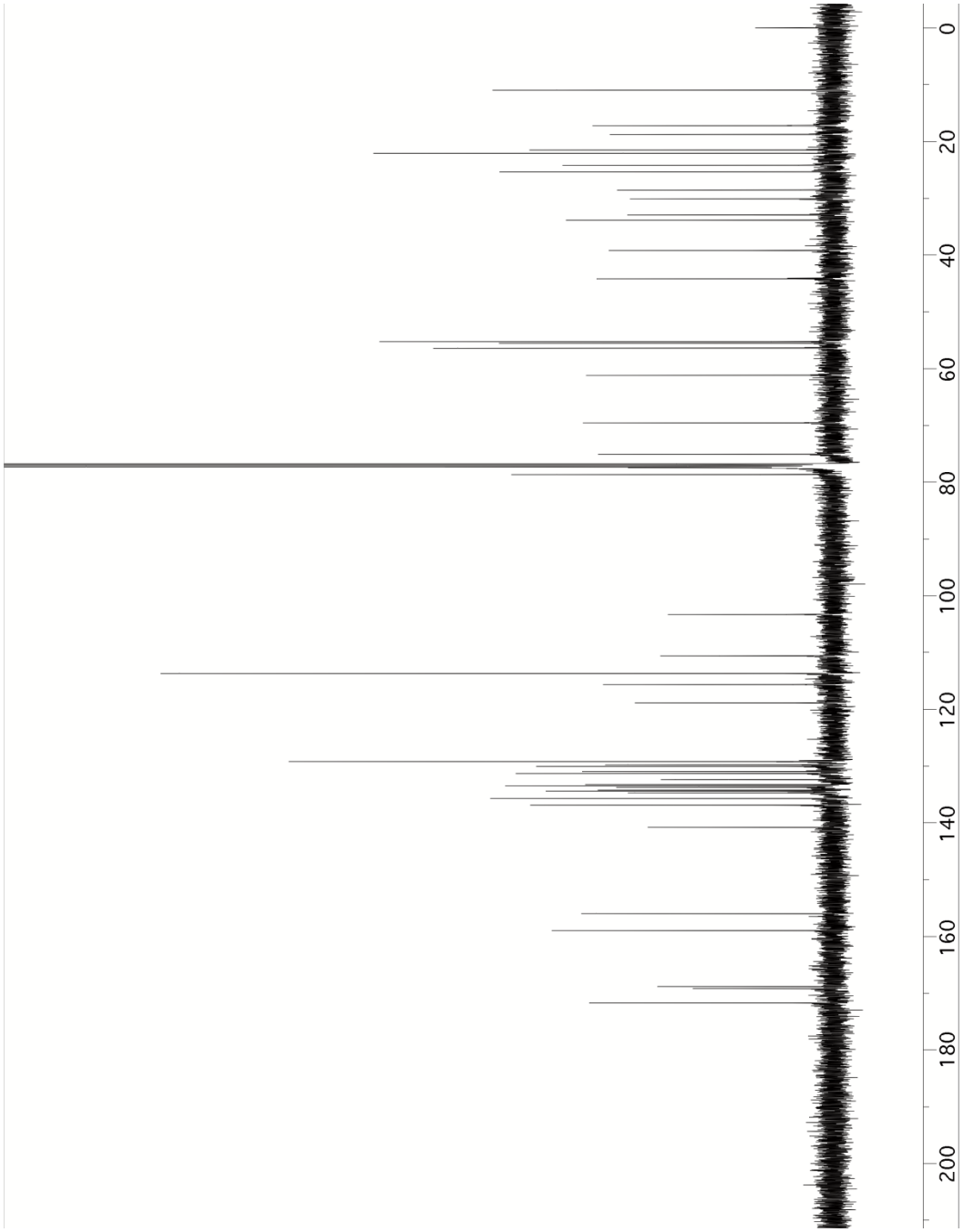


Figure 3.51 ^{13}C NMR spectrum of cytotrienin A bis(diene) **3.55**

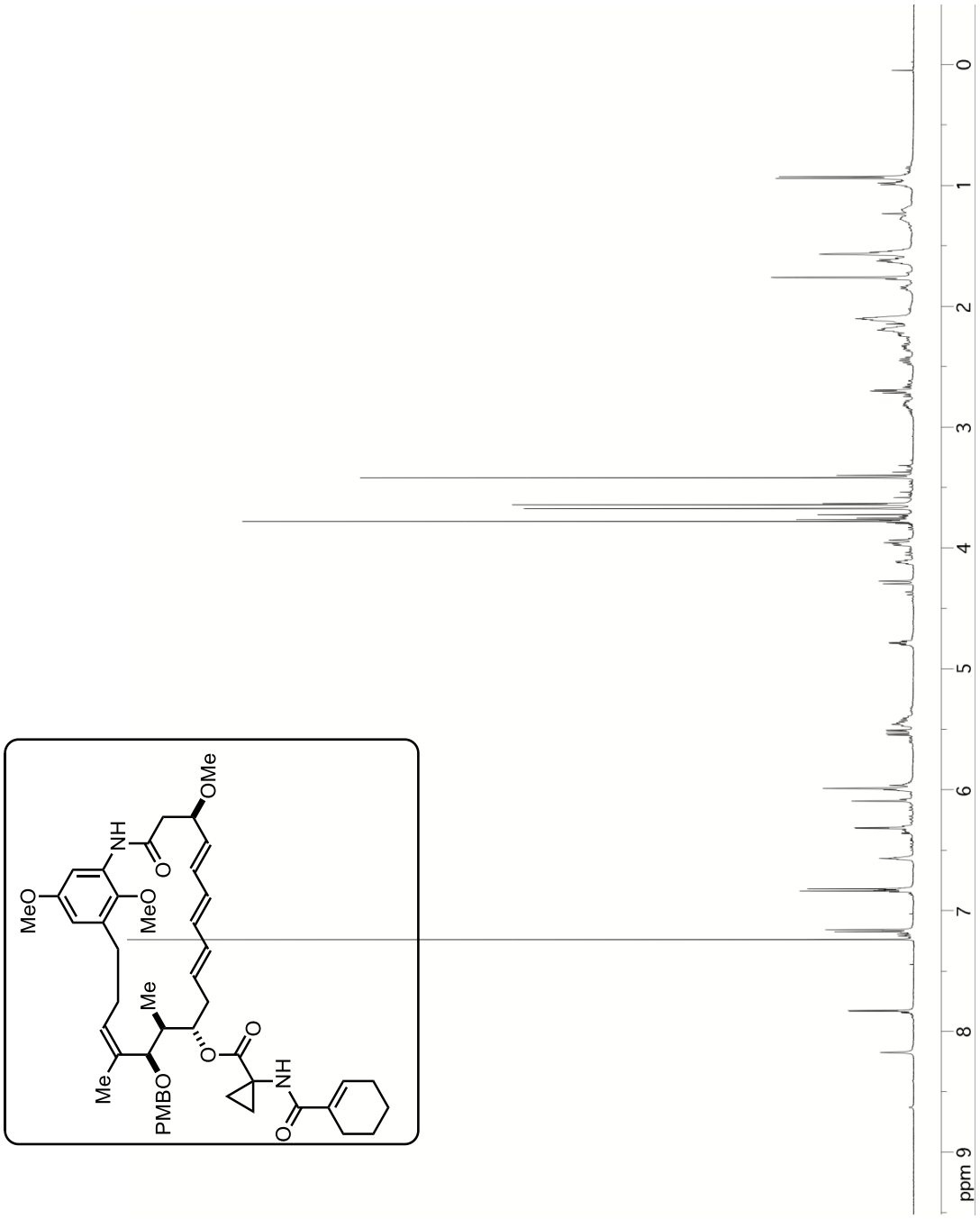


Figure 3.52 ^{1}H NMR spectrum of cytotrienin A core **3.56**

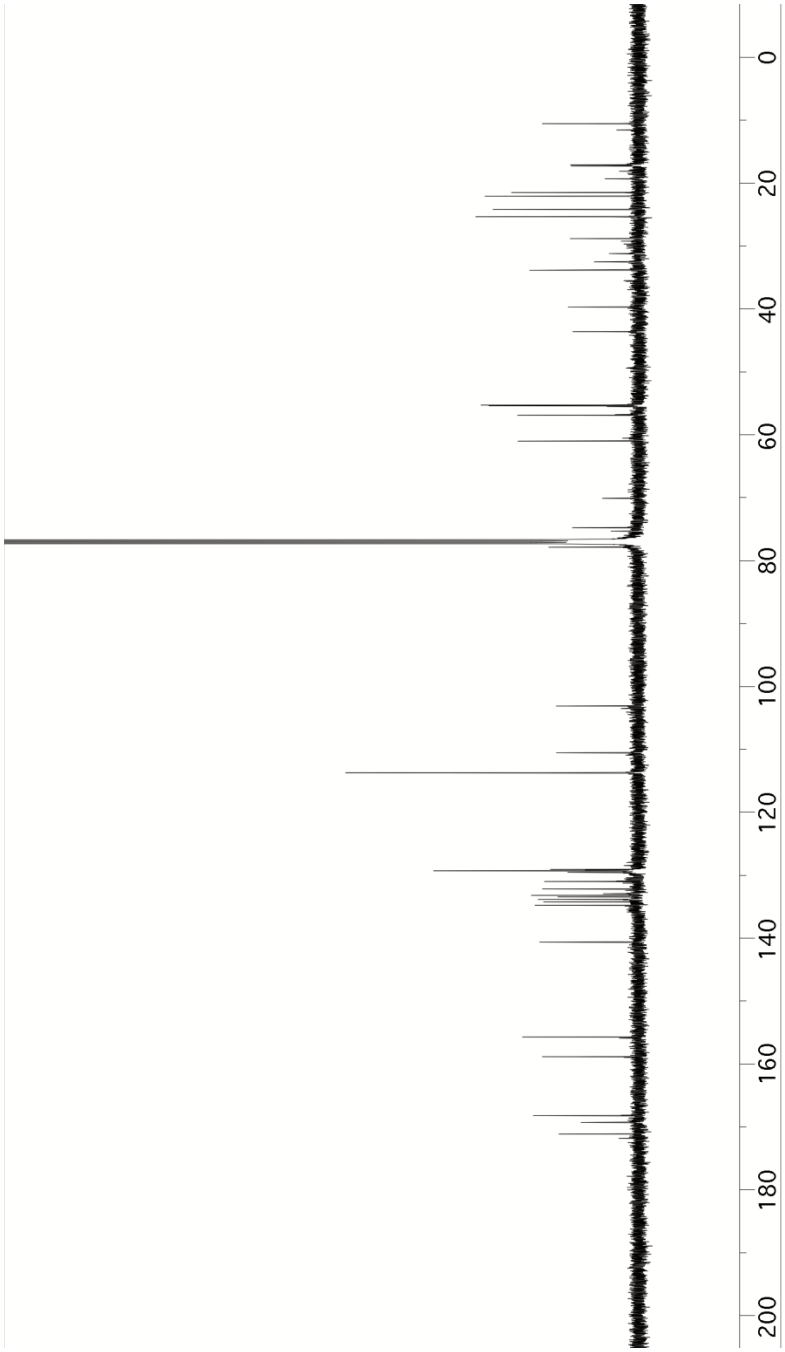


Figure 3.53 ^{13}C NMR spectrum of cytotrienin A core **3.56**

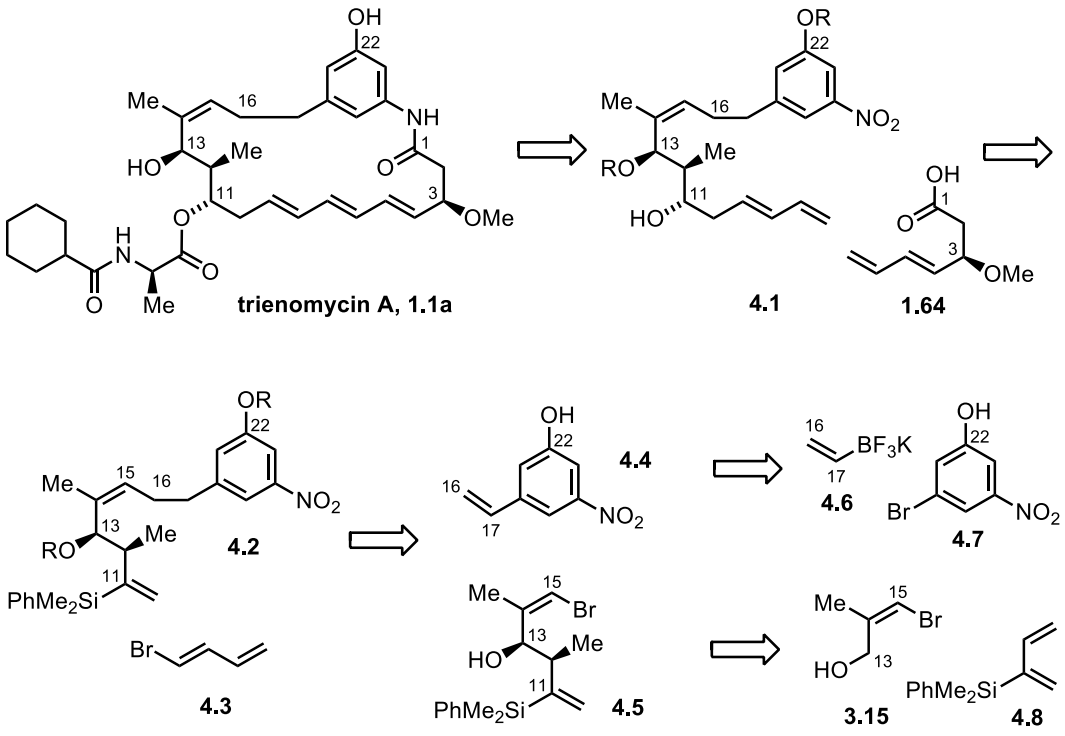
4 SYNTHESIS OF TRIENOMYCIN A AND F

4.1 Initial efforts toward trienomycin A

After our synthetic studies on the C17-benzene ansamycins resulted in a synthesis of the cytotrienin A core **3.56**, we recognized two areas in need of improvement. It would be ideal[130] to use a *syn*-crotylation in the stereotriad construction, thus avoiding a Mitsunobu inversion to correct the C13 stereocenter after the C-C bond formation event.[131] To this end, the second generation C17-benzene ansamycin synthesis would employ an enantioselective ruthenium-catalyzed alcohol CH-*syn*-crotylation[89] for that purpose. The other modification would be in the endgame strategy. During our studies towards cytotrienin A (**1.6a**) we were able to construct all of the C-C bonds in the target natural product, but were unable to achieve the final deprotection. At the onset of the second generation route we also chose to change the target to trienomycin A (**1.1a**). This would allow us to evaluate the generality of our route toward the other members of this class of natural products and pursue a new protecting group strategy.

Our retrosynthetic analysis of trienomycin A (**1.1a**) would employ strategies and fragments from our previous routes that were effective. The pivotal bond disconnections were envisioned at the C11 side chain, a diene-diene RCM, and at the C1 amide providing two major fragments: alcohol **4.1** and acid **1.64** (Scheme 4.1). Since we did not know, which protecting group strategy would be required in the final steps of our route, we initially planned to install silyl ethers at the C13 and C22 hydroxyl groups. The stereotriad of fragment **4.1** could be constructed from adduct **4.2**, through a

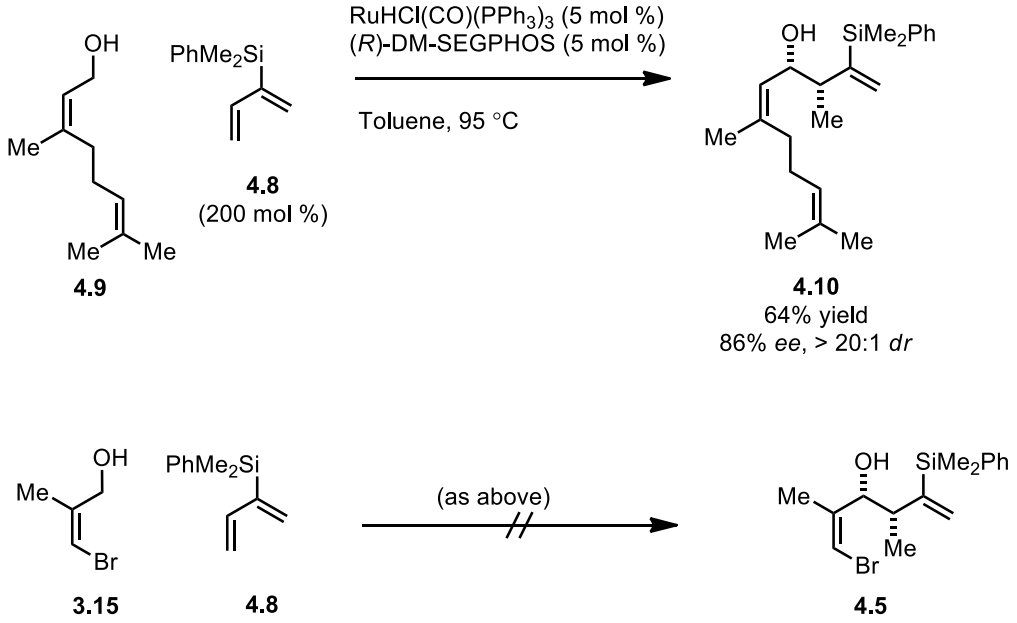
diastereoselective hydroboration to set the C11 stereochemistry, a Suzuki cross-coupling to diene **4.3** and a Fleming-Tamao oxidation.[89] Further disconnection of adduct **4.2** through a Suzuki reaction at C15-C16 would require access to nitro styrene **4.4** and vinyl bromide **4.5**. Again, using a Suzuki disconnection nitro styrene **4.4** would be assembled from potassium ethenyltrifluoroborate salt **4.6** and aryl bromide **4.7**. The keystone of this approach would be implementation of an enantioselective ruthenium-catalyzed alcohol CH-*syn*-crotylation, which we envisioned would construct alcohol **4.5** from vinyl bromide **3.15** and silyldiene **4.8**.



Scheme 4.1 Initial retrosynthesis for trienomycin A (**1.1a**)

We first explored the coupling of vinyl bromide **3.15** with silyldiene **4.8** under conditions previously described for enantioselective ruthenium-catalyzed alcohol

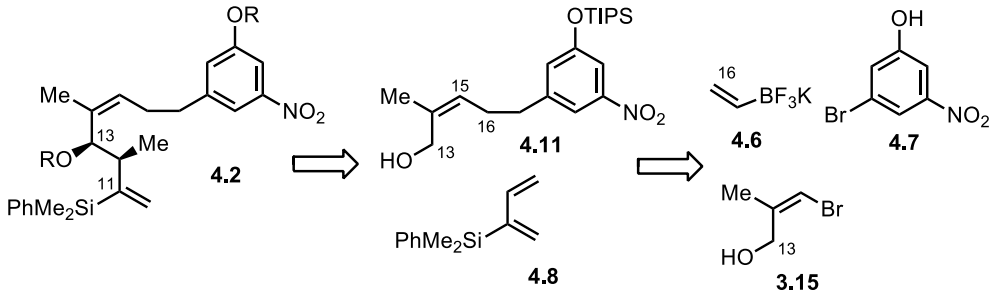
CH-*syn*-crotylation (Scheme 4.2).[89] Krische and co-workers previously demonstrated that the coupling of nerol **4.9** and silyldiene **4.8** to furnish alcohol **4.10** in moderate yield and in high selectivity. However, upon treatment of a mixture of bromide **3.15** with silyldiene **4.8** under *syn*-selective reaction conditions the coupling product **4.5** was not observed. This lack of reactivity required us to pursue an alternate route to intermediate **4.2**.



Scheme 4.2 Unsuccessful application of ruthenium-catalyzed crotylation

4.1.1 REVISED ROUTE FOR INTERMEDIATE 4.2

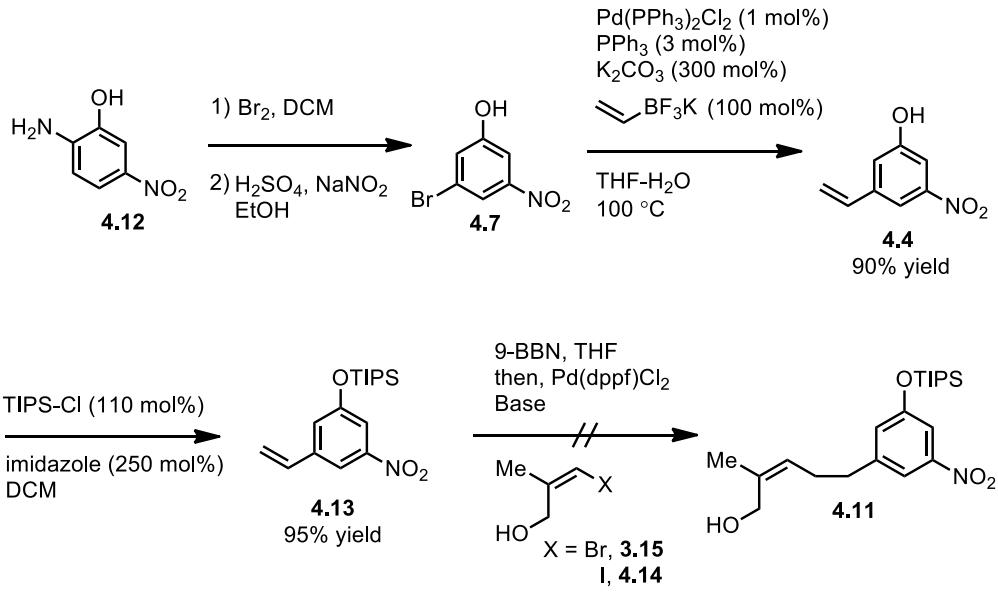
Undeterred by our initial failure, we revised our route to intermediate **4.2** by reordering the steps to access alcohol **4.11** (Scheme 4.3). With alcohol **4.11** we could determine if removing the bromide at C15 would permit the *syn*-crotylation to occur. Our initial investigation focused on developing a route to access **4.11** without a protecting group, at the C13 hydroxyl group.



Scheme 4.3 Revised retrosynthesis of intermediate **4.2**

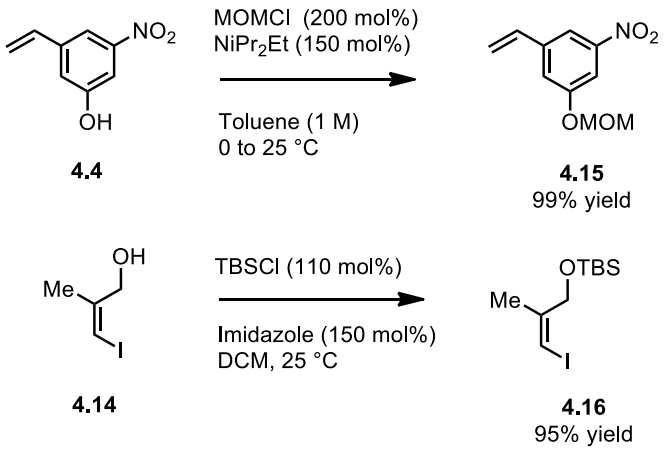
Bromination of nitro arene **4.12** followed by exposure to sulfuric acid and sodium nitrite furnished commercially available bromoarene **4.7** (Scheme 4.4). Suzuki cross-coupling of bromoarene **4.7** with potassium vinyltrifluoroborate **4.6** delivered nitro styrene **4.4** in 90% yield. With this route large quantities of nitro styrene **4.4** were accessible. Reaction of nitro styrene **4.4** with chlorotriisopropylsilane furnished TIPS ether **4.13** in 95% yield. Unfortunately, the one-pot hydroboration Suzuki cross-coupling of nitro sytrene **4.13** and vinyl bromide **3.15** or vinyl iodide **4.14** was a fruitless endeavor. Furthermore, model studies to hydroborate/cross-couple nitro sytrene **4.13** with simple alkenyl halides were not sucessful. We attributed the poor reactivity to the lability of the

TIPS ether under the reaction conditions, and subsequently considered other protecting groups for the phenolic hydroxyl group.



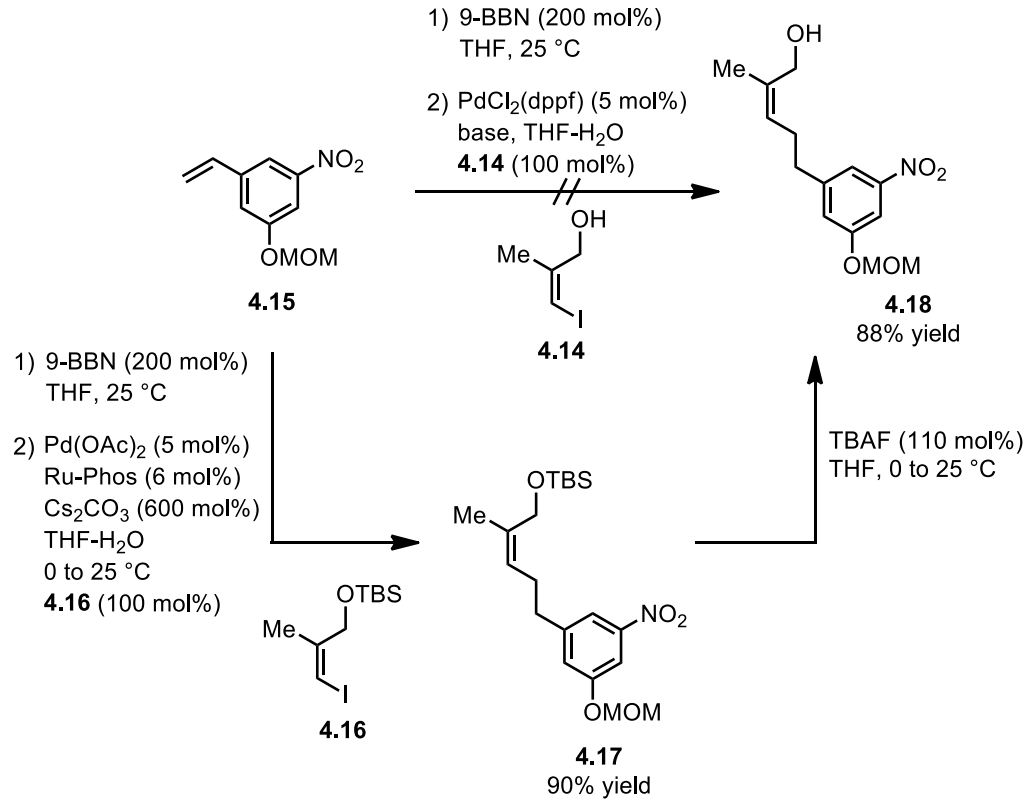
Scheme 4.4 Efforts toward alcohol **4.11**

Since it seemed that a C13 protecting group was necessary and that the C22 TIPS protection was ineffective in any cross-coupling, we revised our protecting group strategy. Using orthogonal protecting groups we would be able to investigate the cross-coupling and selectively deprotect the C13 hydroxyl to access our target intermediate. To that end, phenol **4.4** was treated with chloromethyl methyl ether to furnish MOM ether **4.15** (Scheme 4.5). Exposure of vinyl iodide **4.14** to *tert*-butyldimethylchlorosilane provided TBS ether **4.16**. With both coupling partners in hand we would be able explore their union.



Scheme 4.5 Synthesis of intermediates **4.15** and **4.16**

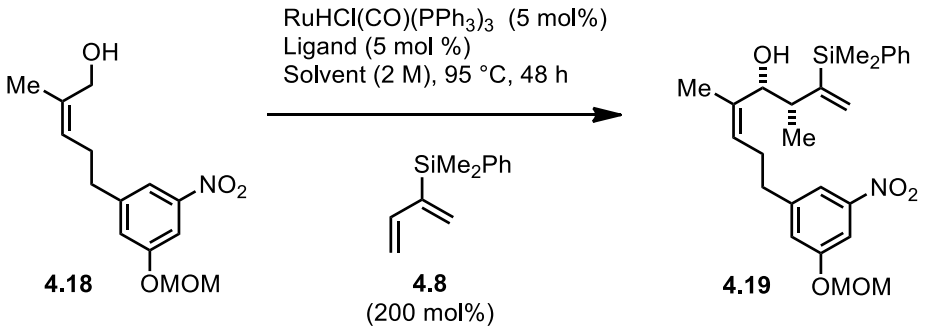
We revisited the possibility of a direct coupling of nitro styrene **4.15** and vinyl iodide **4.14** at the beginning of our exploration of the Suzuki coupling (Scheme 4.6). Unfortunately, the desired coupling product was not detected. We changed our focus toward the cross-coupling of nitro styrene **4.15** and TBS ether **4.16**. Using catalytic $Pd(dppf)Cl_2$ allowed the desired adduct **4.17** to be isolated in 32% yield. Exploration of other catalyst/ligand systems led to the discovery that $Pd(OAc)_2$ and Ru-Phos would deliver adduct **4.17** in 90% yield. Deprotection of the TBS ether with TBAF afforded the target alcohol **4.18** in 88% yield.



Scheme 4.6 Revised route to alcohol **4.18**

With alcohol **4.18** in hand, we set out to install the C12-C13 stereocenters using an enantioselective ruthenium-catalyzed alcohol CH-*syn*-crotylation. Exposure of alcohol **4.18** to silyldiene **4.8**, catalytic $RuHCl(CO)(PPh_3)_3$, and a phosphine ligand furnished the alcohol **4.19** (Scheme 4.7). Unfortunately the reaction produced a mixture of products: including *syn-anti* diastereomers and products of *Z* to *E* isomerization (entry 1). This was an unexpected result, as none of the prior examples of this transformation had such low diastereoselectivity. The alkene isomerization likely occurred from the intermediate aldehyde generated in the course of the reaction (Figure 2.6). An adjustment

of reaction solvent and chiral ligand furnished alcohol **4.19** in modest yield and selectivity (entry 4). The mixture of isomers was carried forward in the synthesis so that we could determine the viability of the current route to intermediate **4.1**.

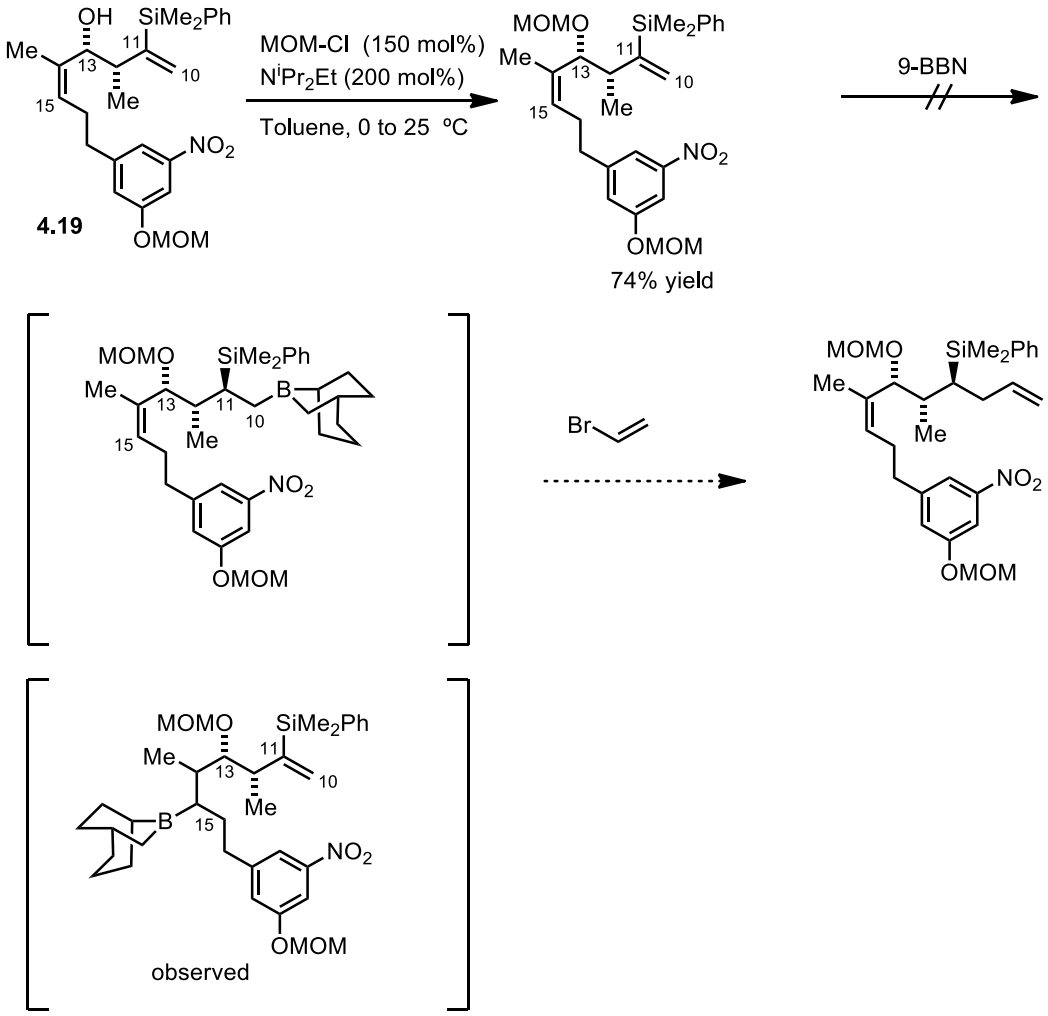


Entry	Solvent	Ligand	*Z*:*E*	dr	Yield
1	Toluene	*rac*-BINAP	3:1	6:1	39%
2	Toluene	(*R*)-Segphos	2:1	9:1	43%
3	Toluene	(*R*)-DM-Segphos	4:1	5:1	54%
4	THF	(*R*)-DM-Segphos	5:1	8:1	65%

Scheme 4.7 Application of ruthenium-catalyzed *syn*-crotylation

With alcohol **4.19** in hand, we set out to construct the C11-C13 stereotriad by utilizing a one-pot diastereoselective hydroboration Suzuki cross-coupling. To facilitate this transformation we chose to protect the C11 hydroxyl group of alcohol **4.19** as a MOM ether (Scheme 4.8). This would also play a role in our endgame strategy, as bis(MOM) protection might allow a single step deprotection in the final step under mild acidic conditions. Although we intended to hydroborate across the C11-C10 bond, NMR experiments indicated that the C14-C15 bond underwent hydroboration first. We were

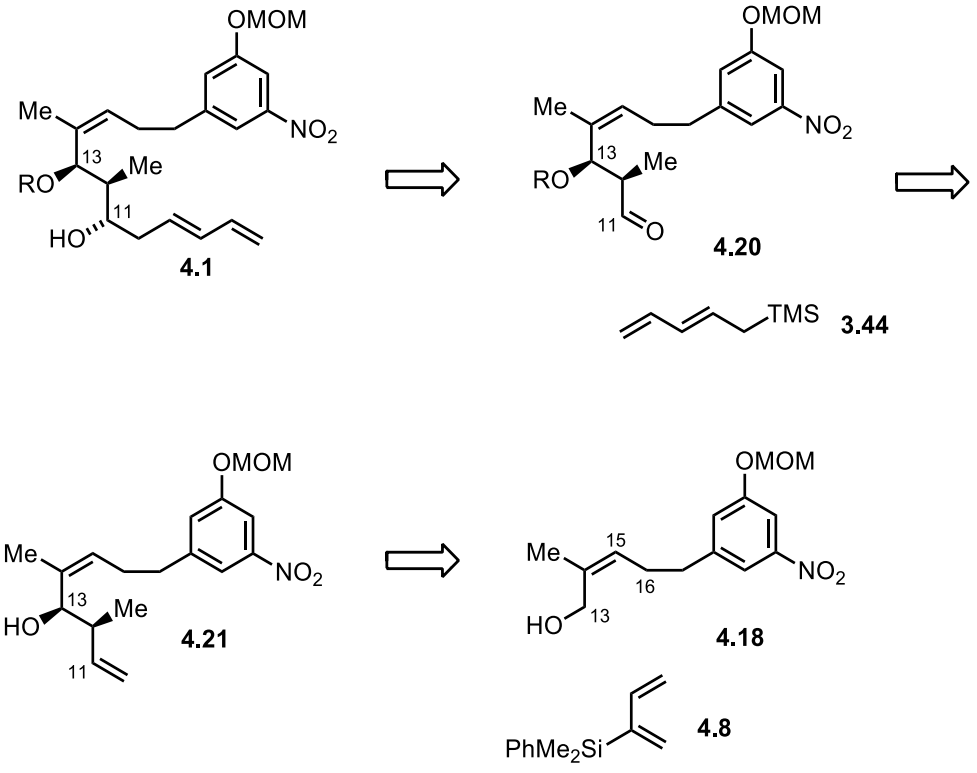
unable to overcome this difference in chemoselectivity, consequently a revision of the route was required.



Scheme 4.8 Unsuccessful diastereoselective hydroboration

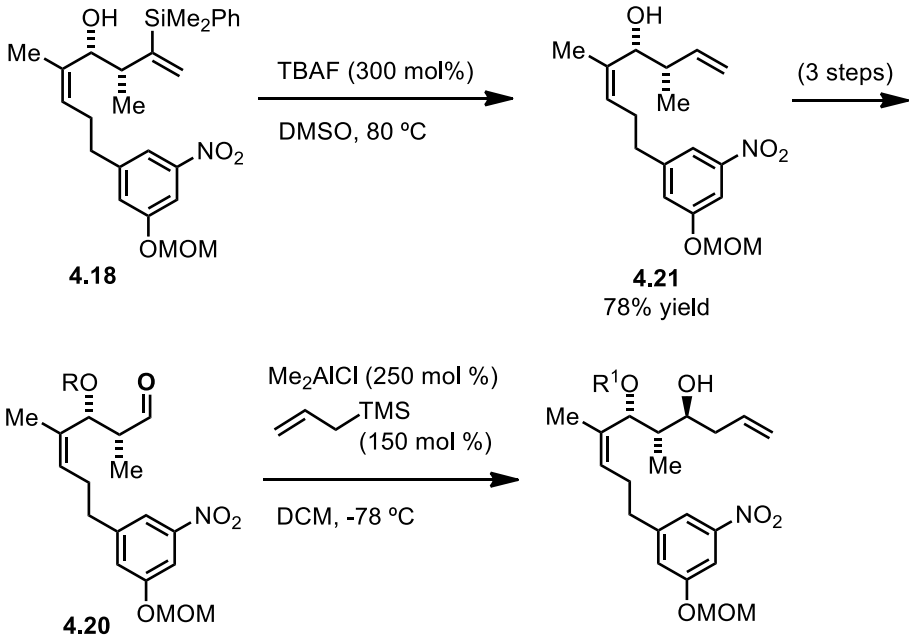
4.2 Revised route for fragment 4.1

Returning to a chelation strategy to set the C11 stereocenter, we sought to obtain **4.1** through a chelation controlled addition of **3.44** to aldehyde **4.20** (Scheme 4.9). At this junction we were unsure, which protecting group on the C13 hydroxyl group would be optimal, or which group could be cleaved at the final stages of the synthesis. Several groups would need to be explored in the chelation controlled addition and subsequently tested in a model system to ensure cleavage would be possible. To that end, aldehyde **4.20** would be accessed from alcohol **4.21**, which in turn could be constructed from alcohol **4.18** and silyldiene **4.8**.



Scheme 4.9 Revised route to alcohol **4.1**

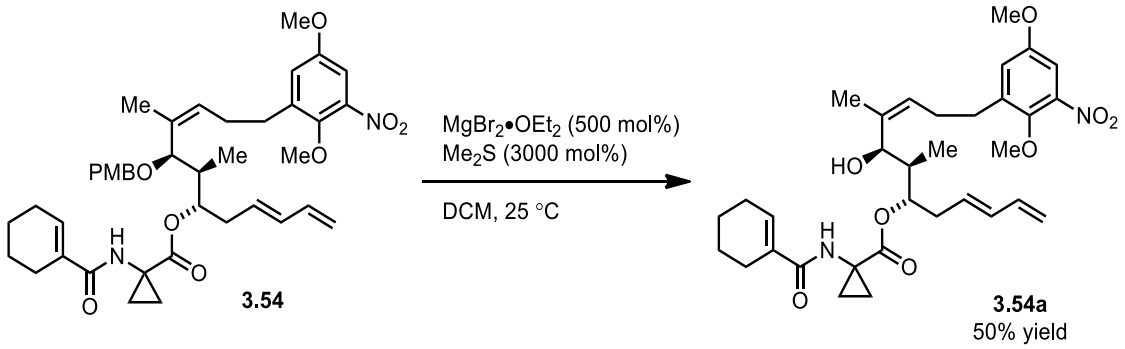
To begin our investigation of protecting groups at the C13 hydroxyl, we first effected a proto-desilylation of alcohol **4.19** with TBAF to furnish alcohol **4.21** (Scheme 4.10). From alcohol **4.21** we were able to gain access to the protected aldehydes in three steps using a protection, dihydroxylation, oxidative cleavage sequence. We investigated how changes at the C13 position would affect yield and selectivity in the chelation controlled addition with allyltrimethylsilane. Our first choice was to evaluate an acid sensitive ether group, subsequently MOM ether **4.22** was isolated in modest yield and poor selectivity. Next we explored a silyl protecting group, and TES ether **4.23** was isolated in both low yield and selectivity. Our top two options for hydroxyl protecting group, with regards to ease of deprotection in the final steps, were unsuitable for the allylation reaction. Revisiting the PMB group we found that PMB ether **4.24** was isolated in both modest yield and high selectivity. Given our inability to deprotect the PMB ether in cytotrienin A, we were reluctant to forge ahead in the synthesis with a PMB ether in the C13 position.



R^1	Yield	dr
MOM, **4.22**	45%	1.7:1
TES, **4.23**	20%	1:1
PMB, **4.24**	48%	>20:1

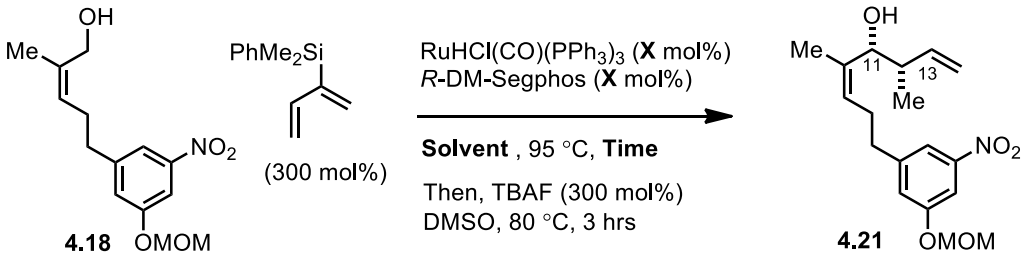
Scheme 4.10 Investigation of the C13 protecting group

Before committing to the PMB ether, we needed some assurance that it could be deprotected later in the synthesis by testing cleavage conditions on a similar system. After inspection of the chemical literature, we became aware of the difficulties associated with cleavage of PMB ethers in the presence of 1,3 dienes.[132] Thus we investigated a model system and found that treatment of intermediate **3.54** with an excess of magnesium dibromide diethyl ether complex and dimethyl sulfide furnished alcohol **3.54a** in 50% yield (Scheme 4.11).[133] With this result we were confident that a late stage PMB ether deprotection would be possible.



Scheme 4.11 Model system for cleavage of the C13 PMB ether

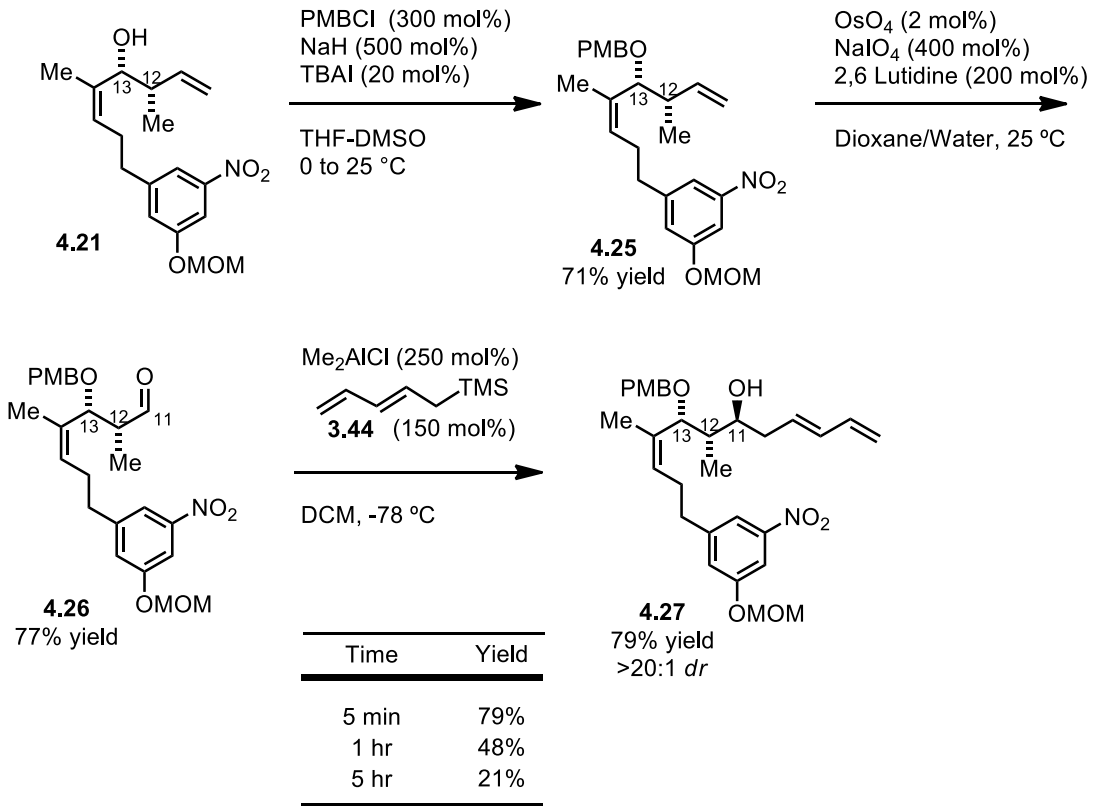
At this stage, we were using two separate steps for crotylation and proto-desilylation to access alcohol **4.21**. In order to further streamline our synthetic route we sought to employ the one-pot crotylation-desilylation protocol (Table 4.1).[89] Our initial investigation of the transformation of alcohol **4.18** under standard conditions afforded alcohol **4.21** in low selectivity and 48% yield (entry 1). An increase of the reaction time resulted in lower selectivity and yield (entry 2). Increasing the catalyst/ligand loading improved selectivity and the yield (entry 3-4). As observed in the previous experiments further increases in the reaction time did not provide additional benefits (entry 5). Due to the high cost of the ligand we continued to investigate conditions at 5 mol% catalyst/ligand loading. By changing the solvent and reaction time the desired product was isolated in high selectivity and modest yield (entry 7-9).



Entry	Solvent	X	Time	*Z*:*E*	dr	Yield
1	THF	5	48	4:1	7:1	48
2	THF	5	72	2:1	5:1	46
3	THF	7	24	7:1	7:1	44
4	THF	7	48	6:1	5:1	69
5	THF	7	72	5:1	4:1	32
6	Dioxane	5	42	5:1	6:1	53
7	Ethyl Acetate	5	42	6:1	8:1	60
→ 8	Ethyl Acetate	5	16	7:1	9:1	64
9	Ethyl Acetate	5	8	9:1	9:1	40

Table 4.1 Optimization of ruthenium-catalyzed *syn*-crotylation

With a reliable method for the preparation of alcohol **4.21**, three steps remained to install the stereotriad and diene. Protection of the C13 alcohol as PMB ether **4.25** followed by oxidative cleavage of the terminal olefin using a modification of the Johnson-Lemieux protocol[134] provided the aldehyde **4.26** in only seven steps from phenol **4.7** (Scheme 4.12). Aldehyde **4.26** was exposed to (*E*)-trimethyl-2,4-pentadienylsilane **3.44** in the presence of Me_2AlCl to generate stereotriad **4.27** via chelation-controlled pentadienylation.[113] Importantly, a short reaction time was necessary to obtain the stereotriad as a single isomer and in high yield.



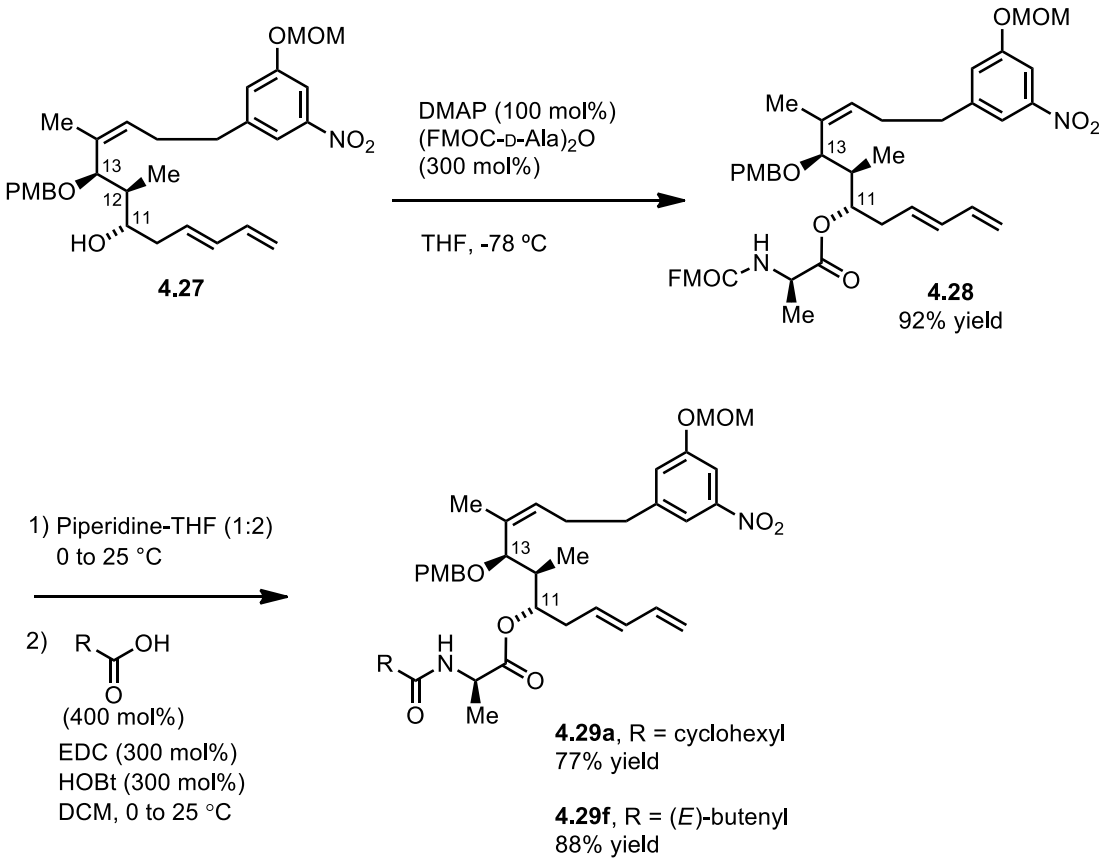
Time	Yield
5 min	79%
1 hr	48%
5 hr	21%

Scheme 4.12 Synthesis of alcohol **4.27**

4.3 Final strategy for trienomycin A and F

With a route in place to access alcohol **4.27**, we were able to elaborate the side chain at C11 with a three step protocol. Accordingly, acylation of the C11 hydroxyl group of **4.27** with the symmetrical anhydride of FMOC-D-alanine to provide ester **4.28** (Scheme 4.13). By introducing different acyl moieties at C11, compound **4.28** serves a common intermediate in the syntheses of trienomycin A and F and potentially other triene-containing C17-benzene ansamycins. Treatment of compound **4.28** with

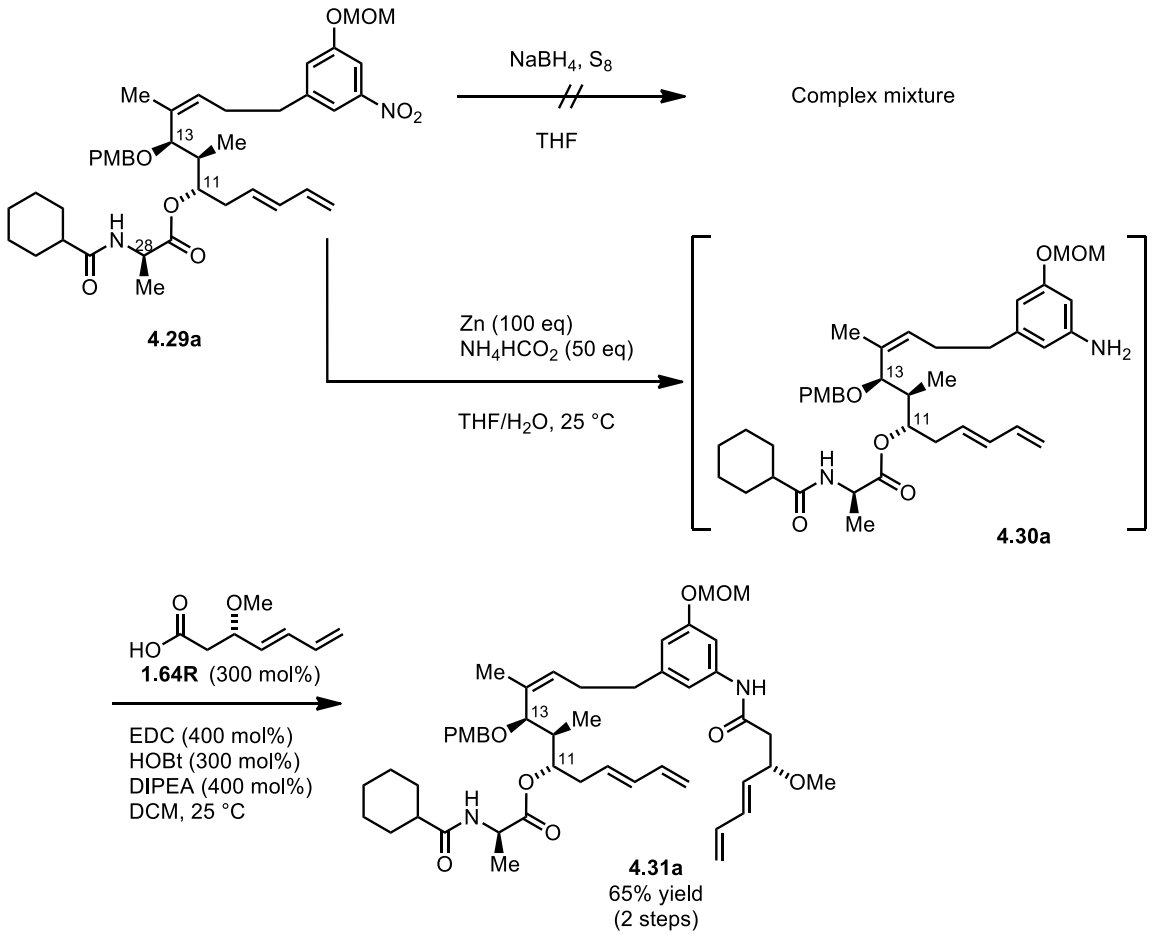
piperidine, followed by the indicated acids permitted formation of amides **4.29a** and **4.29f**.



Scheme 4.13 Elaboration of the C11 side chain

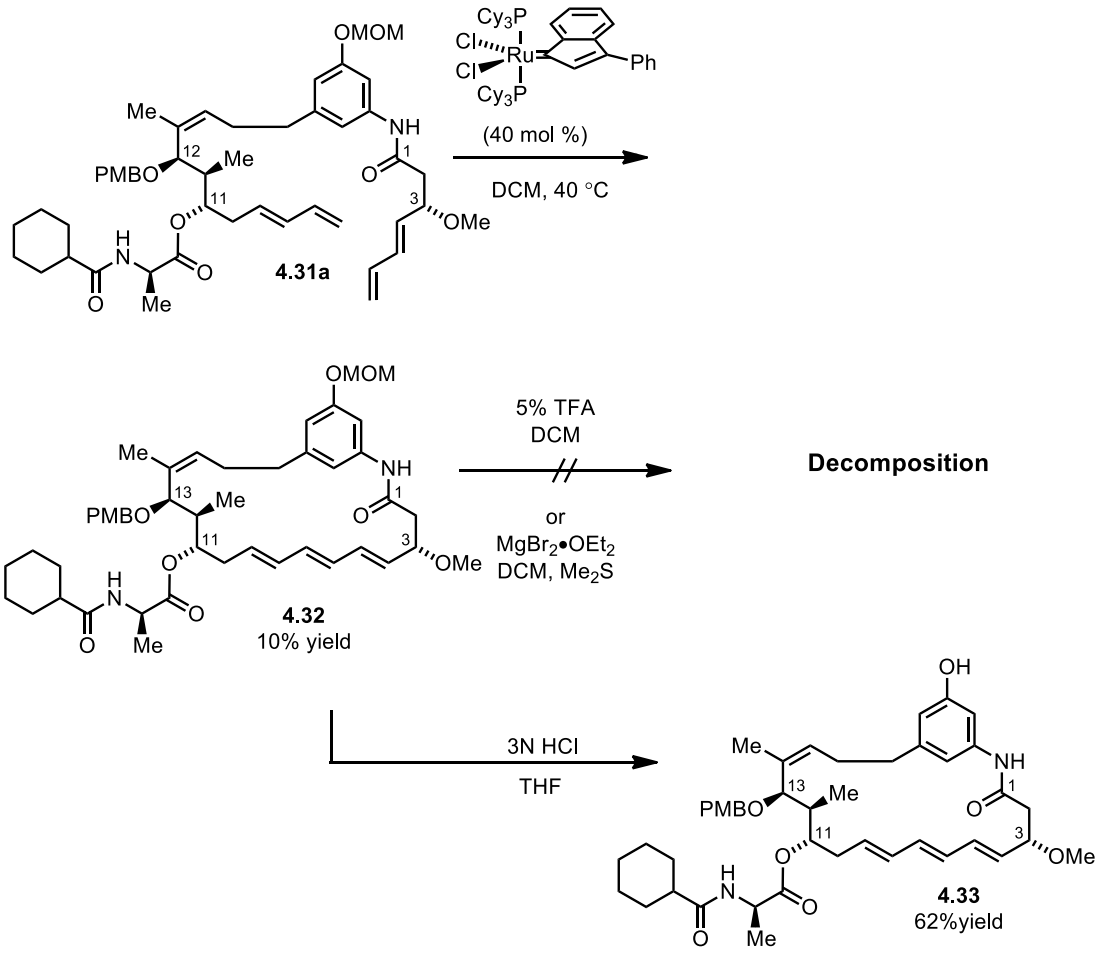
With fragment **4.29a** in hand its union to acid fragment **1.64R** (Scheme 4.14) was explored. As discussed in sections **2.2.2** and **3.2.2.3**, there was an ambiguity in the literature regarding, which stereochemistry would be obtained from a chiral ligand modified catalyst. This led to the construction of acid **1.64R**, which was used in several valuable experiments that ultimately culminated in the successful deprotection strategy. Attempted reduction of the nitro group of **4.29a** with $NaBH_2S_3$[121] provided a complex

mixture of compounds. One plausible explanation for this might be epimerization of the C28 methyl group under the reaction conditions. Browsing the chemical literature revealed an alternative reduction protocol employing mild conditions at room temperature.[135] Accordingly, exposure of nitro arene **4.29a** to an excess of zinc dust and ammonium formate provided an unstable aniline **4.30a**, which was immediately coupled with acid **1.64R** to furnish bis(diene) **4.31a** in 65% yield over two steps.



Scheme 4.14 Synthesis of bis(diene) **4.31a**

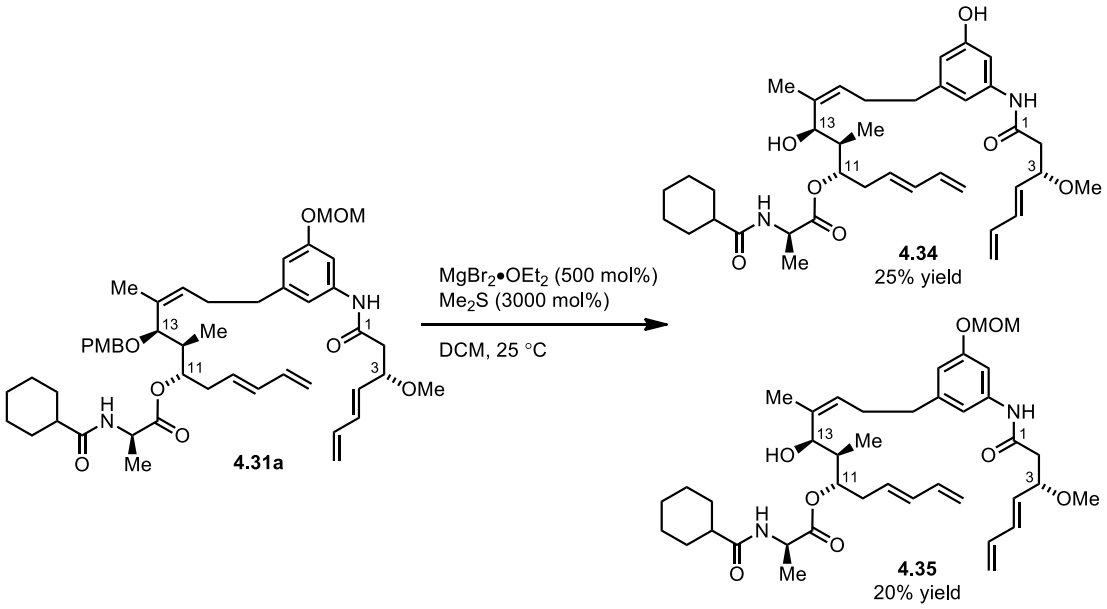
With bis(diene) **4.31a** in hand, the macrocyclization and ether deprotection were all that remained to complete the synthesis. Exposure of bis(diene) **4.31a** to the indenylidene analogue of the first generation Grubbs' metathesis catalyst[124] provided macrocycle **4.32** in 10% yield as a mixture of compounds, with several other RCM products detected by LC/MS (Scheme 4.15). Nevertheless, the small amount of macrocycle **4.32** was subjected to conditions to deprotect the MOM and PMB ethers. Exposure of macrocycle **4.32** to conditions that had worked on a model system (Scheme 4.11) resulted only in decomposition. On a related system Smith and Wan reported conditions for a late stage deprotection of a MOM ether in their synthesis of thiazinotrienomycin E (Scheme 1.14).[30] Fortunately, we were able to employ those acidic conditions to cleave the MOM ether and furnish alcohol **4.33**. Unfortunately, subsequent experiments to deprotect the PMB ether were not successful. It appeared that the C13 PMB ether could not be cleaved after the macrocyclization, and thus we would again revise the route to circumvent this issue.



Scheme 4.15 Initial macrocyclization and deprotection

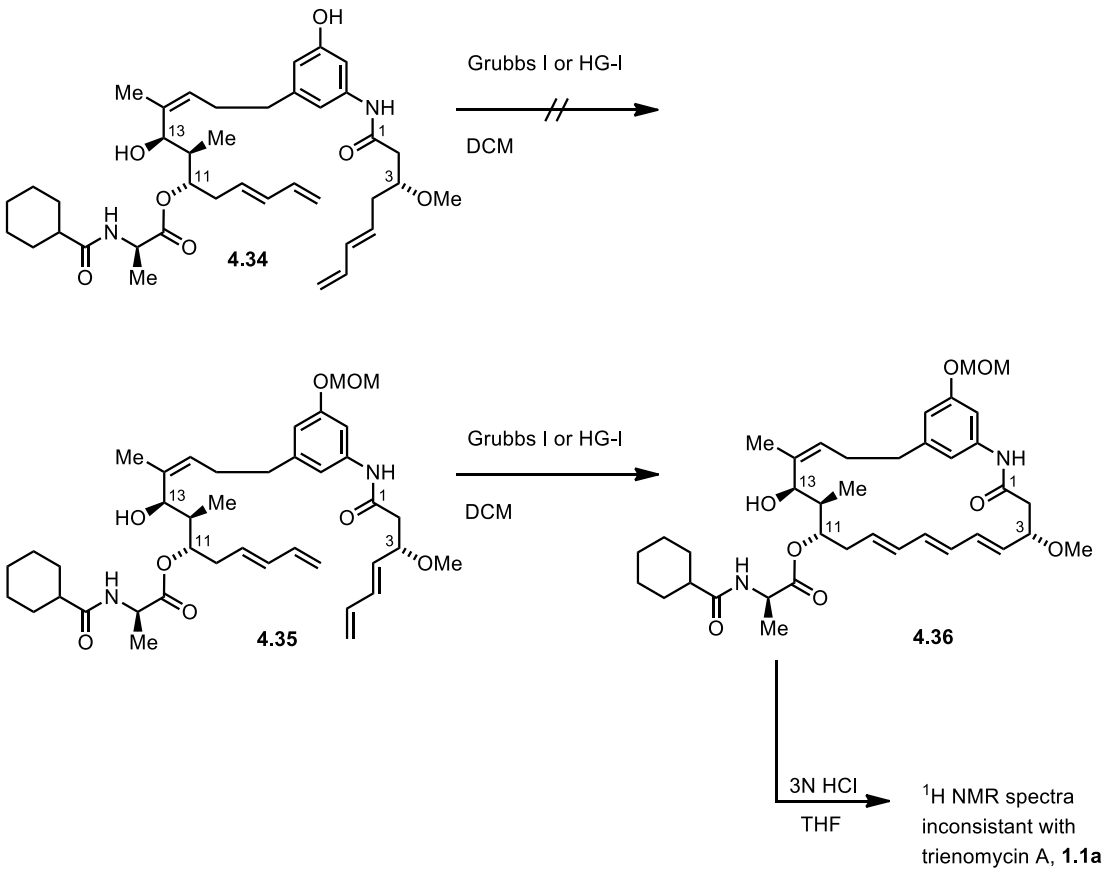
Since we were unable to cleave the C13 PMB ether at the end of the synthetic sequence, we intended to liberate the protecting group before cyclization and carryout the previously established plan. Exposure of the bis(diene) **4.31a** to an excess of magnesium dibromide diethyl ether complex and methyl sulfide furnished two products in low yield: diol **4.34** and alcohol **4.35** (Scheme 4.16). It would be advantageous for the diene-diene RCM to be successful on diol **4.34** because it would allow the natural product to be formed directly without any additional protecting group manipulations. The minor

product, alcohol **4.35** could also be subjected to the RCM, but this would require an additional step to remove the MOM ether.



Scheme 4.16 Late stage deprotection of C11 PMB ether

Diol **4.34** did not productively react in the diene-diene RCM with Grubbs I or Hoveyda-Grubbs I (Scheme 4.17). Only when the catalyst loading was increased above 100 mol% was the starting material consumed. Fortunately, treatment of alcohol **4.35** under RCM conditions did produce a mixture of compounds that was consistent with the desired triene **4.36**. The desired triene macrocycle **4.36** was isolated in 10% yield or less despite changes in concentration, solvent, catalyst, and reaction temperature. The triene product required reverse phase HPLC to separate it from the myriad of products produced in the RCM. After deprotection and reverse-phase HPLC separation, none of the isolated products were consistent with the reported proton NMR spectra of trienomycin A (**1.1a**).

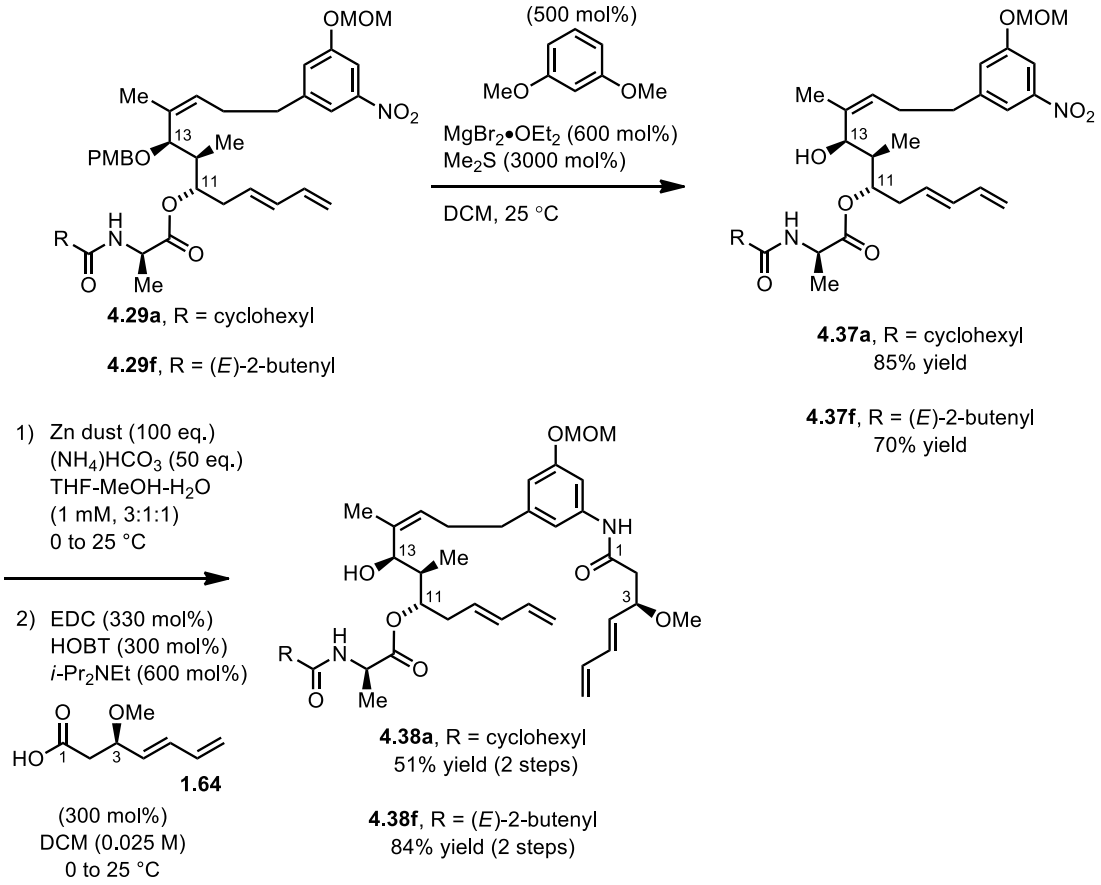


Scheme 4.17 Studies toward macrocyclization and deprotection

We were able to trace this problem to an incorrectly established stereocenter at the C3 position (section **3.2.2.3**) and corrected the problem by synthesizing acid **1.64** with the correct chiral ligand. Despite the *epi*-C3 stereocenter, we were able to access the final product in low yield. To improve the yield of the final steps, we would revise the route again and attempt to access trienomycin A (**1.1a**) in higher yield.

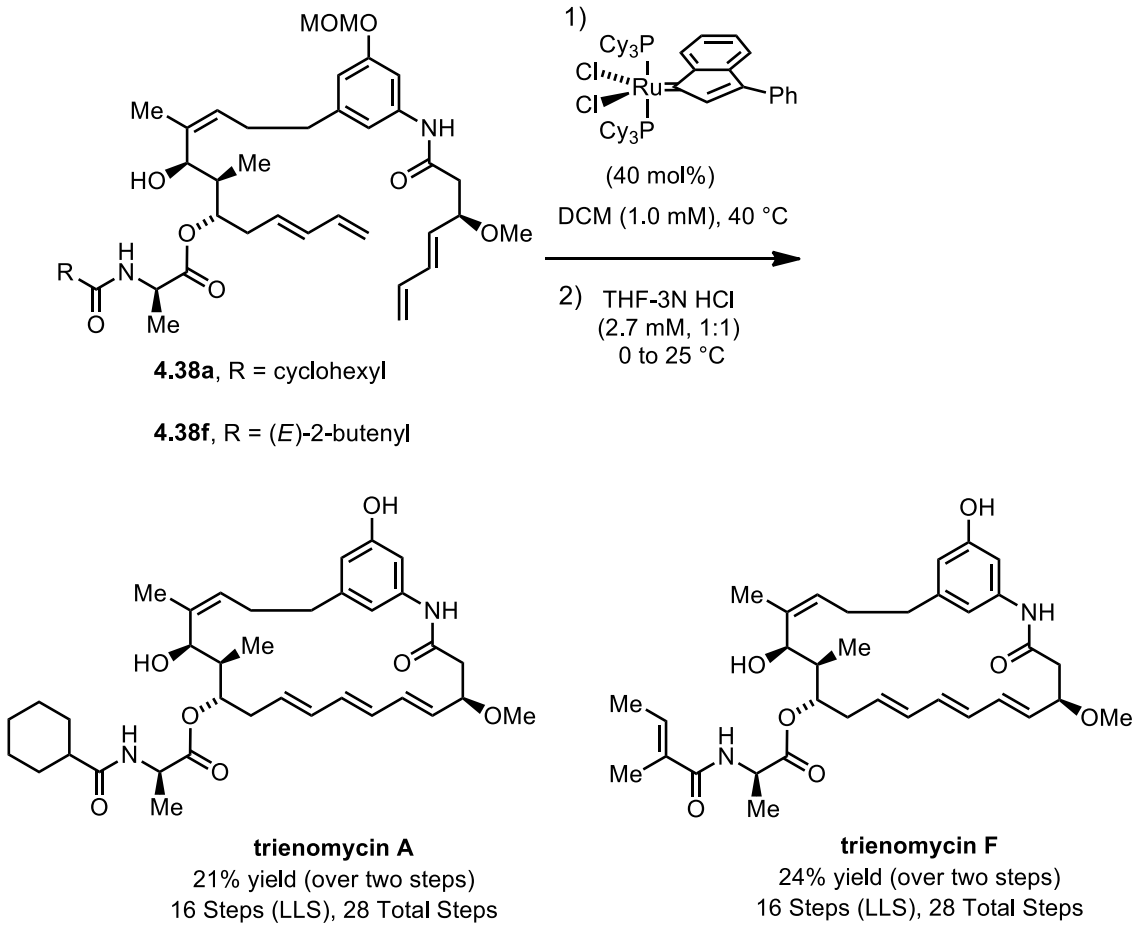
To selectively cleave the C13 PMB ether without affecting the diene moieties or MOM ether, we chose to deprotect intermediates **4.29a** and **4.29f** (Scheme 4.18). Based on the poor results obtained from PMB cleavage of bis(diene) **4.31a** (Scheme 4.16), our

rationale was that it might be more likely to achieve a selective ether cleavage before the nitro reduction. On these substrates cleavage of the PMB ethers was often accompanied with decomposition. To address this issue, we turned to the chemical literature for insight and found that 1,3-dimethoxybenzene[136] was known to act as a scavenger of reactive intermediates in various PMB ether deprotections. Fortunately, the use of 1,3-dimethoxybenzene in our system allowed us to obtain **4.37a** and **4.37f** in good yields. Subsequent reduction of the C20 nitro moieties and acylation of the resulting anilines with acid **1.64** provided the bis(diene) **4.38a** and **4.38f**.



Scheme 4.18 Synthesis of bis(diene) **4.38a** and **4.38f**

Finally, diene-diene RCM to form the triene was explored using Grubbs' first generation catalysts and the Grubbs-Hoveyda-I catalyst. Ring-closing metathesis of **4.38a** and **4.38f** occurred to form a complex mixture of macrocylic products. The indenylidene analogue of the first generation Grubbs' metathesis catalyst,[124] again was more selective for triene formation (Scheme 4.19). In addition to the low yield for the RCM, the subsequent MOM ether cleavage also required HPLC separation to furnish purified natural products in low yield. To circumvent the low yield and poor recovery observed in prior RCM experiments (Scheme 4.17), the RCM reactions were monitored by LC/MS, and the mixture of macrocycles was used directly in the next reaction. The crude mixture was treated with HCl to cleave the MOM ether, and one final reverse phase HPLC purification was performed, thus enabling the 16 step (LLS) total syntheses of trienomycin A and F. This sequence is 14 steps (LLS) shorter than the prior syntheses of trienomycin A and F, and eight steps (LLS) shorter than any prior synthesis of a triene-containing C17-benzene ansamycin.



Scheme 4.19 Synthesis of trienomycin A and F

4.4 Conclusions

By applying C-C bond forming hydrogenation methods, concise syntheses of C17-benzene ansamycins trienomycin A and F were completed. Throughout our synthetic efforts, several key challenges had to be overcome. First, the synthetic route necessitated the expansion of substrate scope for use of this methodology. During the course of our work we found some substrates that contain α-chiral centers or (*Z*)-olefins

might be unsuitable for the hydrogenation methodology. Second, scalability is possible but the high cost and loadings of chiral ligands were a hindrance during scale up. As the cost of chiral ligands comes down and more efficient catalyst systems are developed these methodologies will find greater use.

The success of the final strategy hinged upon three critical observations: (1) the importance of a scavenger in the PMB cleavage, (2) the protocol developed for the RCM, and (3) the Mosher ester study that indicated the C3 stereocenter was incorrectly set. With these advances the synthesis came to a successful end. Although we were able to fruitfully employ the diene-diene RCM, it proved to be highly substrate specific and analogue synthesis should be approached with caution.

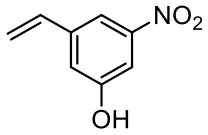
In summary, with the exception of eribulin, a truncated derivative of halichondrin,[137,138,139] all FDA approved polyketides are prepared through fermentation or semi-synthesis, as current synthetic methods cannot concisely address the preparation of such complex structures. Accordingly, the Krische laboratory has devised a suite of catalytic methods for polyketide construction wherein the addition or exchange of hydrogen is accompanied by C-C bond formation.[48,84,85] As illustrated by the present total syntheses of trienomycin A and F,[140] application of this technology has availed the most concise route to any member of this polyketide natural product family.

4.5 Experimental

General Methods

All reactions were run under an atmosphere of argon under anhydrous conditions unless otherwise indicated. Dichloromethane (DCM), 1,2-dichloroethane (DCE), tetrahydrofuran (THF), and toluene (PhMe) were obtained from a Pure-Solv MD-5 Solvent Purification System (Innovative Technology, inc). Anhydrous solvents were transferred using oven-dried syringes. All other commercial reagents were used directly without further purification. Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F254). Visualization of the chromatograms was accomplished using UV light and vanillin, anisaldehyde, permanganate, or cerium molybdate stain with heating. Preparative column chromatography using silica gel was performed according to the method of Still. Infrared spectra were recorded on a Nicolet 380 FTIR. Analytical high performance liquid chromatography (HPLC) spectra were obtained using an Agilent Technologies 1200 series HPLC. Analytical Gas Chromatography (GC) spectra were obtained using an Agilent Technologies 7890A GC system. High-resolution mass spectra (HRMS) were obtained on a Waters Micromass Autospec or a Varian FTICR as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+1, M or M–1) or a suitable fragment ion. Melting points were obtained on a Stuart® melting point apparatus SMP3. Proton nuclear magnetic resonance spectra (1H NMR) were recorded with a Varian spectrometer (400 MHz or 500 MHz) and reported in parts per million (ppm) referenced

to the residual protio solvent signal as an internal standard. Coupling constants are reported in hertz (Hz). Carbon nuclear magnetic resonance spectra (13C NMR) were recorded with a Varian spectrometer (100 MHz or 125 MHz) and reported in parts per million (ppm) referenced to the residual solvent signal as an internal standard. Optical rotations were measured on an ATAGO AP-300 automatic polarimeter at a path length of 1 dm.



3-nitro-5-vinylphenol

A solution of potassium carbonate (38 g, 280 mmol), water (100 mL) was added to a solution of 3-bromo-5-nitrophenol (20 g, 92 mmol), triphenylphosphine (0.72 g, 2.8 mmol), potassium vinyltrifluoroborate (12.3 g, 92 mmol), $PdCl_2(PPh_3)_2$ (0.64 g, 0.92 mmol), tetrahydrofuran (200 mL, 0.5 M) under an atmosphere of argon. The reaction vessel was sealed with a screw cap and heated at 100 °C for 16 h. The resulting solution was cooled to ambient temperature, added to a separatory funnel containing saturated solution of NH_4Cl (100 mL) and brine (200 mL). The resulting mixture was extracted with ethyl acetate (3 x 75 mL). The combined organic extracts were dried over sodium sulfate, filtered, concentrated under reduced pressure, and purified via column chromatography (SiO_2, 10% to 30% ethyl acetate/hexanes, gradient elution) to give the title compound **4.4** (13.7 g, 82.8 mmol, 90% yield) as a yellow solid.

R_f (SiO_2, hexanes/EtOAc = 2 : 1) = 0.3.

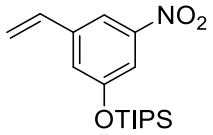
^{1}H NMR (400 MHz; acetone-d_6): δ 9.37 (brs, 1H), 7.80 (s, 1H), 7.56 (s, 1H), 7.34 (s, 1H), 6.82 (dd, *J* = 17.6, 10.9, 1H), 5.97 (d, *J* = 17.6, 1H), 5.42 (d, *J* = 10.9, 1H) ppm.

^{13}C NMR (100 MHz, acetone-d_6): δ 159.1, 150.5, 141.2, 136.0, 119.9, 117.3, 112.9, 110.0 ppm.

FTIR (Neat): λ^{-1} = 3429, 3093, 1618, 1512, 1477, 1344, 1277, 1208, 1159 cm^{-1}.

MS (CI): Calcd. for $C_8H_8NO_3$ (M+H): 166; Found: 166.

MP: 64-65 °C.



triisopropyl(3-nitro-5-vinylphenoxy)silane (4.13)

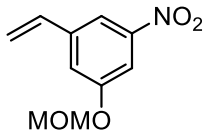
Triisopropylsilyl chloride (4.3 mL, 20 mmol) was added at 25 °C to a mixture of phenol **4.4** (3.0g, 18 mmol), imidazole (3.1g, 45 mmol), and dichloromethane (30 mL). The resulting mixture was stirred at ambient temperature for 16 h, filtered, concentrated under reduced pressure, and purified via column chromatography (SiO_2, 10% ethyl acetate/hexanes) to give the title compound **4.13** (5.57 g, 17.1 mmol, 95% yield) as a yellow oil

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.65 (s, 1H), 7.11 (s, 1H), 6.77 (dd, *J* = 17.5, 10.9, 1H), 5.85 (d, *J* = 17.5, 1H), 5.39 (d, *J* = 10.9, 1H), 1.31 (m, 3H), 1.12 (s, 18H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 140.2, 135.1, 123.8, 114.0, 113.9, 18.1, 12.9 ppm.

FTIR (Neat): λ^{-1} = 3429, 3093, 1618, 1512, 1477, 1344, 1277, 1208, 1159 cm^{-1}.

HRMS (CI): Calcd. for $C_{17}H_{28}NO_3Si$ (M+H): 322.1838; Found: 322.1839.



1-(methoxymethoxy)-3-nitro-5-vinylbenzene (4.15)

A solution of chloromethyl methyl ether (81 mL, 170 mmol, 2.1 M toluene) was added at ambient temperature to a solution of 3-nitro-5-vinylphenol **4.4** (14.0 g, 84.8 mmol) and diethyl ether (30 mL). The resulting solution was cooled to 0 °C and diisopropylethylamine (22 mL, 130 mmol) was added slowly, warmed to ambient temperature and stirred 14 h. The resulting mixture was added to a separatory funnel containing $NaHCO_3$ (100 mL) and organic layer was separated. The aqueous layer was extracted with ether (2 x 30 mL), the organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude reside was purified via column chromatography (SiO_2, 6% to 33% ethyl acetate/hexanes, gradient elution) to give the title compound **4.15** (17.5 g, 84.0 mmol, 99% yield) as a yellow oil.

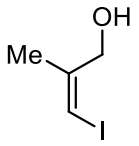
R_f (SiO_2, hexanes/EtOAc = 9 : 1) = 0.54.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.72 (s, 1H), 7.31 (s, 1H), 6.67 (dd, *J* = 17.5, 10.9, 1H), 5.83 (d, *J* = 17.5, 1H), 5.39 (d, *J* = 10.9, 1H), 5.21 (s, 2H), 3.46 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 149.3, 140.1, 134.7, 120.1, 117.2, 114.3, 110.0, 94.5, 56.3 ppm.

FTIR (Neat): λ^{-1} =2958, 1617, 1515, 1347, 1270, 1149 cm^{-1}.

MS (CI): Calcd. for $C_{10}H_{12}NO_4$ (M+H): 210; Found: 210.



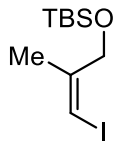
(Z)-3-iodo-2-methylprop-2-en-1-ol (4.14)

According to a literature procedure:[141] propargyl alcohol (5.2 mL, 90 mmol) was added to a solution of copper iodide (1.7 g, 9.0 mmol) and tetrahydrofuran (90 mL, 1.0 M) under N_2, at −20 °C. A solution of methylmagnesium bromide (66 mL, 200 mmol, 3 M diethyl ether) was added slowly. After the addition was complete the reaction vessel was warmed to −10 °C and the solution was stirred for 30 min. A solution of Iodine (22.9 g, 90.0 mmol), diethyl ether (20 mL), and tetrahydrafuran (20 mL) was added to the reaction mixture and the cooling bath was removed. The resulting mixture was added to a separatory funnel containing saturated NH_4Cl (100 mL) and brine (100 mL), extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was

purified by column chromatography (SiO_2, 10–50% DCM/hexanes, gradient elution) to furnish the title compound (13.5 g, 68.2 mmol, 75% yield) as a light yellow oil. The spectral data for the title compound were consistent with reported values.[2]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.96 (s, 1H), 4.22 (s, 2H), 1.95 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 74.7, 67.8, 21.4 ppm.

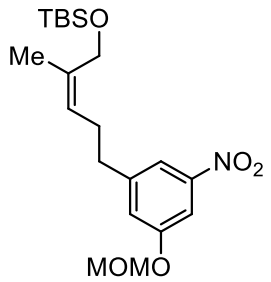


(*Z*)-*tert*-butyl(3-iodo-2-methylallyloxy)dimethylsilane (4.16)

tert-Butyldimethylsilyl chloride was added (11.3 g, 75.0 mmol) to a solution of (Z)-3-iodo-2-methylprop-2-en-1-ol (13.5 g, 68.2 mmol), imidazole (5.11 g, 75.0 mmol), and dichloromethane (120 mL, 0.57 M) under an atmosphere of N_2 at 0 °C. The cooling bath was removed and the reaction was stirred for 16 h at ambient temperature. The resulting mixture was filtered, concentrated, and purified via column chromatography (SiO_2, 18:1:1 to 9:1:1 hexanes-dichloromethane-ethyl acetate, gradient elution) to furnish the title compound **4.16** (20.3 g, 65.0 mmol, 95% yield) as a light yellow oil. The spectral data for the title compound were consistent with reported values.[142]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (s, 1H), 4.24 (s, 2H), 1.90 (s, 3H) 0.91 (s, 9H), 0.09 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.5, 72.3, 68.5, 25.7, 21.3, 18.8, -5.4 ppm.



(*Z*)-*tert*-butyl(5-(3-(methoxymethoxy)-5-nitrophenyl)-2-methylpent-2-enyloxy)dimethylsilane (4.17)

1-(methoxymethoxy)-3-nitro-5-vinylbenzene **4.15** (4.0g, 19 mmol), tetrahydrofuran (50 mL), and 9-borabicyclo[3.3.1]nonane (3.0 g, 24 mmol) were combined under N_2 and stirred at ambient temperature overnight. The resulting solution was cooled to 0 °C and solution of caesium carbonate (31 g, 96 mmol) and water (30 mL) was added, followed by a solution of $Pd(OAc)_2$ (180 mg, 0.80 mmol), 2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl (450 mg, 0.96 mmol), and tetrahydrofuran (50 mL). To the resulting mixture a solution of (*Z*)-*tert*-butyl(3-iodo-2-methylallyloxy)dimethylsilane **3** (5.0 g, 16 mmol) and tetrahydrofuran (30 mL, 0.12 M). The cooling bath was removed and reaction mixture was stirred for 14 h. The reaction mixture was added to a separatory funnel containing NH_4Cl (100 mL), water (200 ml), and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried with sodium sulfate, filtered, concentrated under reduced pressure, and purified via column chromatography (SiO_2, 18:1:1 to 9:1:1 hexanes-dichloromethane-ethyl acetate, gradient elution) to give the title compound **4.17** (5.6g, 14 mmol, 90% yield) as a dark brown oil.

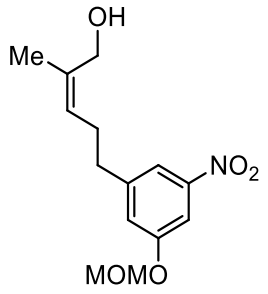
$\underline{R_f}$ (SiO_2, hexanes/EtOAc = 5 : 1) = 0.54.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.70 (s, 1H), 7.15 (s, 1H), 5.25-5.12 (m, 3H), 4.04 (s, 2H), 3.49 (s, 3H), 2.70 (t, *J* = 7.7, 2H), 2.37 (q, *J* = 7.4, 2H), 1.73 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 145.0, 136.6, 124.4, 122.9, 116.9, 108.8, 94.6, 61.8, 56.3, 36.0, 29.0, 26.0, 21.2, 18.4, -5.2 ppm.

FTIR (Neat): λ^{-1} = 2928, 2855, 1748, 1532, 1450, 1349, 1268, 1251, 1216, 1149, 1076, 1018 cm^{-1}.

MS (CI) Calcd. for $C_{20}H_{33}NO_5Si$ (M-): 395; Found: 395.



(*Z*)-5-(3-(methoxymethoxy)-5-nitrophenyl)-2-methylpent-2-en-1-ol (4.18)

Tetra-n-butylammonium fluoride (31 mL, 31 mmol, 1 M tetrahydrofuran) was added to a solution of (*Z*)-*tert*-butyl(5-(3-(methoxymethoxy)-5-nitrophenyl)-2-methylpent-2-enyloxy)dimethylsilane (11.0 g, 27.8 mmol) and tetrahydrofuran (150 ml, 0.15 M) under N_2 at 0 °C, the cooling bath was removed and the reaction mixture was stirred for 1.5 h. NH_4Cl (100 mL) and Brine (150 mL) were added to the reaction mixture. The resulting mixture was extracted with diethyl ether (3 x 100 mL), the organic extracts were combined, dried with magnesium sulfate, filtered, and concentrated under reduced

pressure. The crude residue was purified via column chromatography (SiO_2, 10% to 30% ethyl acetate/hexanes, gradient elution) to give the title compound **4.18** (6.90 g, 24.5 mmol, 88% yield) as a light brown solid.

R_f (SiO_2, hexanes/EtOAc = 3 : 1) = 0.2.

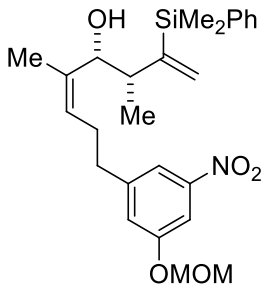
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (t, *J* = 2.2, 1H), 7.69 (s, 1H), 7.16 (s, 1H), 5.30 (t, *J* = 7.3, 1H), 5.22 (s, 2H), 4.04 (s, 2H), 3.49 (s, 3H), 2.73 (t, *J* = 7.5, 2H), 2.41 (q, *J* = 7.4, 2H), 1.79 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 149.1, 144.8, 136.1, 126.2, 122.8, 116.9, 108.9, 94.5, 61.4, 56.4, 35.9, 28.8, 21.3 ppm.

FTIR (Neat): λ^{-1} = 3332, 2968, 2937, 1738, 1582, 1536, 1454, 1344, 1267, 1151, 1086, 1002 cm^{-1}.

MS (CI): Calcd. for $C_{14}H_{19}NO_5$ (M-): 281; Found: 281.

MP: 35-36 °C.



(3*R*,4*R*,*Z*)-2-(dimethyl(phenyl)silyl)-8-(3-(methoxymethoxy)-5-nitrophenyl)-3,5-dimethylocta-1,5-dien-4-ol (4.19)

In a screw cap vial ethyl acetate (1.0 mL, 2.1M) and 2-(dimethyl(phenyl)silyl)-1,3-butadiene[143] (1.0 g, 5.3 mmol) were added to (*Z*)-5-(3-(methoxymethoxy)-5-nitrophenyl)-2-methylpent-2-en-1-ol **4** (600 mg, 2.1 mmol), (*R*)-(+)-5,5′−Bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole (77 mg, 0.107 mmol), and $RuHCl(CO)(PPh_3)_3$[144] (102 mg, 0.107) under and atmosphere of argon. The reaction vessel was sealed with a screw cap and heated at 95 °C for 16 h.. After cooling to ambient temperature, the resulting mixture concentrated under reduced pressure, and purified via column chromatography (SiO_2, 5% to 15% ethyl acetate/hexanes, gradient elution) to give the title compound **4.19** (550 mg, 1.1 mmol, 55% combined yield) with a diastereomeric ratio of 12:1 (*syn*:*anti*) and a 7:1 (*Z*:*E*) mixture of alkene isomers as a yellow oil. . The stereochemical assignment was inferred based on analogy with the literature precedent.[89]

R_f (SiO_2, hexanes/EtOAc = 4 : 1) = 0.55.

$[\alpha]_{24}^{D}$= 38 (c = 1.10, $CHCl_3$).

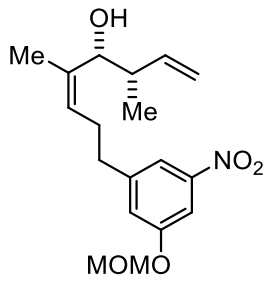
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (t, J = 2.2, 1H), 7.67 (s, 1H), 7.50-7.48 (m, 2H), 7.35-7.29 (m, 3H), 7.15 (s, 1H), 5.81 (d, J = 1.3, 1H), 5.61 (d, J = 2.2, 1H), 5.22 (s, 2H),

5.11-5.08 (m, 1H), 4.30 (d, J = 6.6, 1H), 3.49 (s, 3H), 2.72-2.59 (m, 2H), 2.57-2.47 (m, 1H), 2.31-2.19 (m, 3H), 1.53 (s, 3H), 1.03 (d, J = 6.9, 3H), 0.39 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 153.3, 149.2, 145.1, 137.9, 137.6, 134.1, 129.3, 127.9, 127.3, 125.9, 122.8, 117.0, 109.0, 94.6, 72.5, 56.5, 41.8, 35.9, 28.9, 19.5, 16.6, -2.3, -2.5 ppm.

FTIR (Neat): λ^{-1} = 3468, 2958, 1530, 1451, 1349, 1268, 1149, 1011 cm^{-1}.

MS (CI) Calcd. for $C_{26}H_{35}NO_5Si$: 469; Found: 469.



(3*S*,4*R*,*Z*)-8-(3-(methoxymethoxy)-5-nitrophenyl)-3,5-dimethylocta-1,5-dien-4-ol

(4.21)

In a screw cap vial ethyl acetate (1.0 mL, 2.1M) and 2-(dimethyl(phenyl)silyl)-1,3-butadiene[143] (1.2 g, 6.3 mmol) were added to (*Z*)-5-(3-(methoxymethoxy)-5-nitrophenyl)-2-methylpent-2-en-1-ol **4** (600 mg, 2.1 mmol), (*R*)-(+)-5,5′−Bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole (108 mg, 0.150 mmol), and $RuHCl(CO)(PPh_3)_3$[144] (142 mg, 0.150) under and atmosphere of argon. The reaction vessel was sealed with a screw cap and heated at 95 °C for 16 h. After cooling to ambient temperature, dimethyl sulfoxide (1 mL) and tetra-n-butylammonium fluoride (6.3 mL, 6.3 mmol, 1 M in tetrahydrofuran)

were added. The reaction vessel was sealed with a screw cap and heated at 80 °C for 3 h. After cooling to ambient temperature, the resulting mixture was added to a separatory funnel containing NH_4Cl (20mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried with sodium sulfate, filtered, concentrated under reduced pressure, and purified via column chromatography (SiO_2, 5% to 25% ethyl acetate/hexanes, gradient elution) to give the title compound **4.21** (460 mg, 1.3 mmol, 64% combined yield) with a diastereomeric ratio of 9:1 (*syn*:*anti*) and a 7:1 (*Z*:*E*) mixture of alkene isomers as a yellow oil. The stereochemical assignment was inferred based on analogy with the literature precedent.[89]

R_f (SiO_2, hexanes/EtOAc = 4 : 1) = 0.25.

$[\alpha]_{24}^{D}$= 158 (c = 1.50, $CHCl_3$).

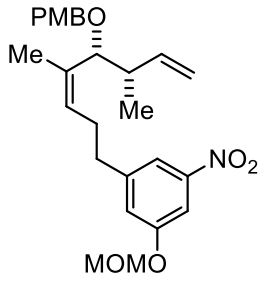
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.69 (s, 1H), 7.16 (s, 1H), 5.56 (ddd, *J* = 17.4, 10.2, 7.4, 1H), 5.23 (d, *J* = 13.7, 3H), 5.02 (d, *J* = 17.2, 1H), 4.95 (d, *J* = 10.4, 1H), 4.17 (d, *J* = 8.8, 1H), 3.49 (s, 3H), 2.72 (q, *J* = 6.9, 3H), 2.44-2.33 (m, 3H), 1.69 (s, 3H), 1.11 (d, *J* = 6.6, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 149.2, 144.9, 140.0, 137.3, 126.9, 122.8, 117.0, 114.7, 109.0, 94.6, 73.7, 56.5, 41.8, 35.9, 28.7, 18.2, 16.3 ppm.

FTIR (Neat): λ^{-1} = 3468, 2958, 1530, 1451, 1349, 1268, 1149, 1011 cm^{-1}.

MS (CI) Calcd. for $C_{18}H_{25}NO_5$: 335; Found: 335.

HPLC (Chiralcel OJ–H, OJ–H, OJ–H column, 10-30% *i*-PrOH/hexanes, gradient elution 0-15 min, 0.5 mL/min, 280 nm): t_{minor} = 33.96 min, t_{major} = 34.75 min; *ee* = 90%.



1-((5*R*,6*S*,*Z*)-5-(4-methoxybenzyloxy)-4,6-dimethylocta-3,7-dienyl)-3-(methoxymethoxy)-5-nitrobenzene (4.24)

Sodium hydride (720 mg, 18 mmol) was added to a mixture of (3S,4R,Z)-8-(3-(methoxymethoxy)-5-nitrophenyl)-3,5-dimethylocta-1,5-dien-4-ol **6** (1.2 g, 3.6 mmol), dimethyl sulfoxide (5 mL), tetrahydrofuran (20 mL, 0.14 M), tetra-n-butylammonium iodide (130 mg, 0.35 mmol), and 4-methoxybenzyl chloride (1.7 g, 11 mmol) under an atmosphere of nitrogen. The cooling bath was removed and the mixture was stirred for 3 h. The reaction mixture was added to NH_4Cl (50 mL), extracted with ethyl acetate (3 x 25 mL), the combined organic extracts were washed with brine (10 mL), and concentrated onto SiO_2 under reduced pressure. The crude reside was purified via column chromatography (SiO_2, 5% to 20% ethyl acetate/hexanes, gradient elution) to give the title compound **4.24** (1.4 g, 3.1 mmol, 87% yield) as a yellow oil.

R_f = (SiO_2, hexanes/EtOAc = 9 : 1) = 0.5.

$[\alpha]_{24}^{D}$= 21 (c = 1.0, $CHCl_3$).

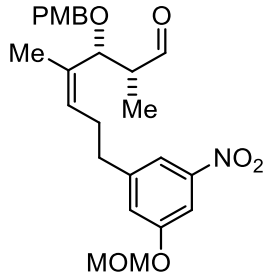
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (t, *J* = 2.2, 1H), 7.68 (t, *J* = 1.7, 1H), 7.22-7.20 (m, 2H), 7.13 (t, *J* = 1.8, 1H), 6.88-6.86 (m, 2H), 5.52 (ddd, *J* = 17.3, 10.3, 7.6, 1H), 5.43 (t, *J* = 7.1, 1H), 5.20 (s, 2H), 4.99 (d, *J* = 17.2, 1H), 4.90 (d, *J* = 11.2, 1H), 4.32 (d, *J* = 11.5,

1H), 4.03 (d, *J* = 11.5, 1H), 3.80 (s, 3H), 3.48 (s, 3H), 2.76-2.63 (m, 2H), 2.45-2.23 (m, 4H), 1.67 (s, 3H), 1.13 (d, *J* = 6.6, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 157.6, 149.1, 144.9, 140.0, 135.0, 130.8, 129.2, 128.8, 123.0, 116.8, 114.2, 113.7, 108.6, 94.5, 79.9, 69.4, 56.3, 55.2, 40.6, 36.0, 28.9, 18.1, 17.0 ppm.

FTIR (Neat): λ^{-1} = 2958, 1612, 1584, 1530, 1512, 1452, 1349, 1246, 1149, 1077, 1030, 1013 cm^{-1}.

HRMS (CI): Calc for $C_{26}H_{33}NO_6$ (M): 455.2308; Found 455.2308.



2*R*,3*R*,*Z*)-3-(4-methoxybenzyloxy)-7-(3-(methoxymethoxy)-5-nitrophenyl)-2,4-dimethylhept-4-enal (4.26)

1-((5*R*,6*S*,*Z*)-5-(4-methoxybenzyloxy)-4,6-dimethylocta-3,7-dienyl)-3-(methoxymethoxy)-5-nitrobenzene (405 mg, 0.89 mmol), dioxane (15 mL, 0.06 M), and water (5 mL) were combined and vigorously stirred at ambient temperature. 2,6–Lutidine (0.20 mL, 1.8 mmol), and osmium tetratoxide (1.8 mL, 0.036 mmol, 0.02 M *tert*-butanol) were added, followed by sodium periodate (570 mg, 2.7 mmol). The resulting mixture was vigorously stirred at ambient temperature for 17.5 h, filtered, extracted with

dichloromethane (3 x 20 mL), and the combined organic extracts were concentrated under reduced pressure (water bath under 20°C). The crude reside was purified via column chromatography (SiO_2, 1:1 dichloromethane/hexanes) to give the title compound **4.26** (310 mg, 0.69 mmol, 77% yield) as a yellow oil.

R_f (SiO_2, hexanes/EtOAc = 4: 1) = 0.5.

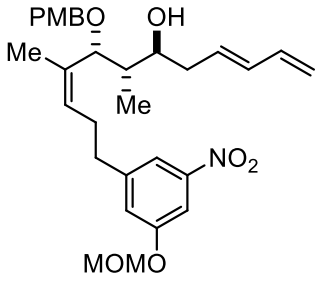
$[\alpha]_{23}^{D}$= 28 (c = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz; acetone-d^6): δ 9.53 (s, 1H), 7.74 (t, *J* = 1.6, 1H), 7.68 (t, *J* = 2.2, 1H), 7.32 (t, *J* = 1.7, 1H), 7.20 (d, *J* = 8.8, 2H), 6.88 (d, *J* = 8.7, 2H), 5.59 (t, *J* = 7.1, 1H), 5.29 (s, 3H), 4.45 (d, *J* = 8.0, 1H), 4.27 (d, *J* = 11.4, 1H), 4.07 (d, *J* = 11.4, 1H), 3.77 (s, 3H), 3.44 (s, 3H), 2.67-2.62 (m, 1H), 2.53 (dd, *J* = 15.1, 7.8, 1H), 2.38 (q, *J* = 9.4, 1H), 1.71 (s, 3H), 1.07 (d, *J* = 6.8, 3H) ppm.

^{13}C NMR (100 MHz, acetone-d^6): δ 203.0, 160.0, 158.5, 149.8, 146.0, 134.5, 131.2, 130.6, 129.8, 123.9, 117.3, 114.2, 108.9, 95.2, 76.6, 69.9, 56.2, 55.3, 50.3, 36.0, 29.5, 18.6, 10.6 ppm.

FTIR (Neat): λ^{-1} = 2936, 1723, 1530, 1513, 1452, 1302, 1246, 1149, 1079, 1029, 1013 cm^{-1}.

MS (CI): Calcd. for $C_{25}H_{30}NO_7$ (M-H): 456; Found: 456.



(3*E*,6*S*,7*S*,8*R*,9*Z*)-8-(4-methoxybenzyloxy)-12-(3-(methoxymethoxy)-5-nitrophenyl)-7,9-dimethyldodeca-1,3,9-trien-6-ol (4.27)

Dimethyl aluminium chloride (2.1 mL, 2.1 mmol, 1 M hexanes) was added to a solution of intermediate **4.26** (380 mg, 0.83 mmol) in dichloromethane (12 mL, 0.07 M) under an atmosphere of N_2 at −78 °C. After 2 min (*E*)-trimethyl(penta-2,4-dien-1-yl)silane (174 mg, 1.25 mmol) was added to the orange solution. The resulting mixture was stirred for 5 min at −78 °C. Methanol (1 mL) was added to the reaction mixture, followed by a 10% citric acid solution (5 mL) and a 10% dipotassium phosphate solution (10 mL). The reaction mixture was warmed to ambient temperature, added to a separatory funnel, and extracted with chloroform (2 x 25 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified via column chromatography (SiO_2, 1:1:8 to 1:1:3 dichloromethane/diethyl ether/hexanes, gradient elution) to give the title compound **4.27** (340 mg, 0.65 mmol, 78% yield) with a diastereomeric ratio of >20:1 as a light yellow oil. The stereochemical assignment was inferred based on analogy with the literature precedent.[113]

R_f (SiO_2, hexanes/EtOAc = 4 : 1) = 0.4.

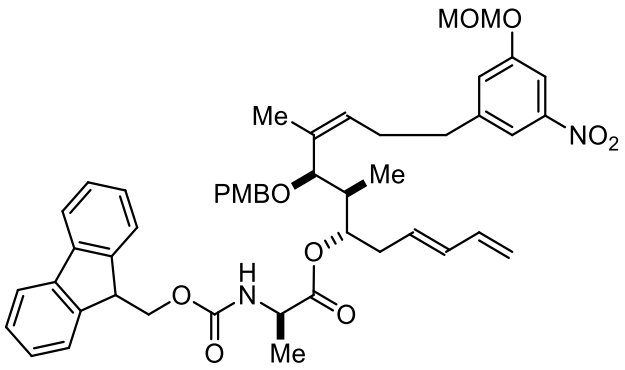
$[\alpha]_{23}^{D}$= 34.6 (c = 1.00, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 (t, *J* = 2.2, 1H), 7.68 (t, *J* = 1.6, 1H), 7.19 (d, *J* = 8.6, 2H), 7.14 (t, *J* = 1.8, 1H), 6.87 (d, *J* = 8.6, 2H), 6.29 (dt, *J* = 16.9, 10.3, 1H), 6.05 (dd, *J* = 15.3, 10.4, 1H), 5.66 (dt, *J* = 15.0, 7.4, 1H), 5.44 (t, *J* = 7.2, 1H), 5.20 (s, 2H), 5.08 (d, *J* = 16.9, 1H), 4.97 (d, *J* = 10.3, 1H), 4.32 (d, *J* = 11.4, 1H), 4.26 (d, *J* = 5.3, 1H), 4.02 (d, *J* = 11.4, 1H), 3.79 (s, 3H), 3.54 (quintet, *J* = 5.8, 1H), 3.47 (s, 3H), 2.77-2.67 (m, 3H), 2.42 (dq, *J* = 15.1, 7.6, 1H), 2.33-2.28 (m, 1H), 2.16 (t, *J* = 6.7, 2H), 1.76 (s, 4H), 0.97 (d, *J* = 7.0, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 159.3, 157.6, 149.1, 144.7, 136.9, 135.7, 135.5, 131.2, 130.0, 129.4, 128.2, 122.9, 116.8, 115.6, 113.8, 108.7, 94.5, 77.6, 73.5 70.0, 56.3, 55.2, 41.8, 37.9, 35.9, 29.0, 19.9, 12.2 ppm.

FTIR (Neat): λ^{-1} = 3450, 2936, 1530, 1513, 1452, 1349, 1302, 1246, 1149, 1079, 1029, 1010 cm^{-1}.

HRMS (CI): Calcd. for $C_{30}H_{39}NO_7$ (M): 525.2727; Found: 525.2730.



(*R*)-(3*E*,6*S*,7*S*,8*R*,9*Z*)-8-((4-methoxybenzyl)oxy)-12-(3-(methoxymethoxy)-5-nitrophenyl)-7,9-dimethyldodeca-1,3,9-trien-6-yl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanoate (4.28)

Fmoc-D-alanine hydrate (1.55g, 4.71 mmol), molecular sieves (1.0 g), and dichloromethane (50 mL) were combined under N_2 stirred vigorously at ambient temperature for 1 h and cooled to 0 °C. N,N'-Dicyclohexylcarbodiimide (486 mg, 2.36 mmol) was added to the reaction mixture, the cooling bath was removed, and the mixture was vigorously stirred for 1 h at ambient temperature. The resulting mixture was filtered, the filter cake was rinsed with dichloromethane (3 x 20 mL) and the filtrate was concentrated under reduced pressure. Tetrahydrofuran (10 mL) was added to the white residue, the reaction vessel was cooled to −78 °C. A solution of (3*E*,6*S*,7*S*,8*R*,9*Z*)-8-(4-methoxybenzyloxy)-12-(3-(methoxymethoxy)-5-nitrophenyl)-7,9-dimethyldodeca-1,3,9-trien-6-ol **4.27** (413 mg, 0.785 mmol),, tetrahydrofuran (10 mL), and 4-dimethylaminopyridine (96 mg, 0.79 mmol) was added to the reaction mixture. The resulting solution was stirred for 3 h at −78 °C. Phosphate buffer solution (3 mL, pH =7) was added and cooling bath was removed. The reaction mixture was added to a

separatory funnel containing $NaHCO_3$ (15 mL) and extracted with $CHCl_3$ (3 x 50 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified via column chromatography (SiO_2, 1:1:8 to 1:1:3 dichloromethane/diethyl ether/hexanes, gradient elution) to give the title compound **4.28** (590 mg, 0.72 mmol, 92% yield) as a light yellow oil.

R_f (SiO_2, Hexanes/DCM/Ethyl Ether = 3 : 1 : 1) = 0.2.

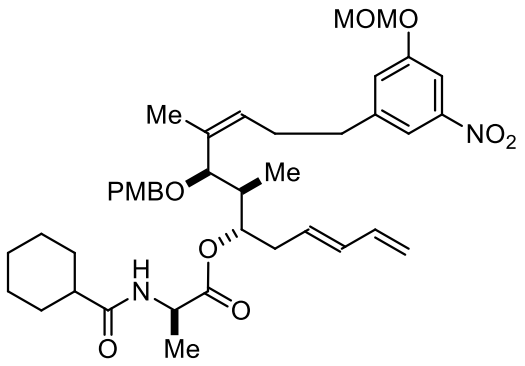
$[\alpha]_{22}^{D}$= 74 (c = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.73 (m, 4H), 7.60 (t, *J* = 8.3, 1H), 7.39 (t, *J* = 7.4, 1H), 7.30 (t, *J* = 7.4, 2H), 7.21 (d, *J* = 8.3, 2H), 7.17 (s, 1H), 6.87 (d, *J* = 8.5, 2H), 6.27 (dt, *J* = 17.0, 10.1, 1H), 6.04 (dd, *J* = 14.9, 10.6, 1H), 5.59-5.51 (m, 3H), 5.16 (s, 2H), 5.10 (d, *J* = 17.0, 1H), 5.01 (d, *J* = 10.2, 1H), 4.99-4.81 (m, 1H), 4.43-4.34 (m, 3H), 4.27 (d, *J* = 11.2, 1H), 4.21 (t, *J* = 7.0, 1H), 4.05-4.00 (m, 2H), 3.77 (s, 3H), 3.45 (s, 3H), 2.79-2.69 (m, 2H), 2.52-2.42 (m, 1H), 2.35-2.25 (m, 2H), 2.12 (dd, *J* = 12.8, 6.4, 1H), 1.83 (s, 3H), 1.38 (d, *J* = 7.0, 3H), 1.07 (d, *J* = 6.8, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 159.0, 155.5, 149.0, 144.6, 143.9, 143.7, 141.2, 136.5, 135.3, 133.9, 130.5, 129.3, 129.1, 128.6, 127.6, 127.0, 125.0, 125.0, 124.9, 122.8, 119.8, 116.6, 116.1, 113.6, 108.6, 94.4, 77.3, 75.2, 69.7, 66.8, 56.2, 55.1, 49.7, 47.1, 39.8, 35.8, 33.5, 29.0, 18.9, 18.6, 11.1 ppm.

FTIR (Neat): λ^{-1} = 2936, 1720, 1612, 1584, 1530, 1513, 1450, 1348, 1302, 1246, 1180, 1150, 1076, 1031, 1010 cm^{-1}.

MS (ESI): Calcd. for $C_{48}H_{54}N_2O_{10}$ (M+ Na^+): 841.4; Found: 841.4.



(*R*)-((3*E*,6*S*,7*S*,8*R*,9*Z*)-8-(4-methoxybenzyloxy)-12-(3-(methoxymethoxy)-5-nitrophenyl)-7,9-dimethyldodeca-1,3,9-trien-6-yl) 2-(cyclohexanecarboxamido)propanoate (4.29a)

Compound **4.28** (300 mg, 0.37 mmol) and tetrahydrofuran (10 mL) were combined under N_2, the reaction vessel was cooled to 0 °C, piperidine (5 mL) was added. The reaction vessel was warmed to ambient temperature and stirred for 30 min. The resulting mixture was concentrated under reduced pressure and azeotroped with toluene (3 x 10 mL). Under an atmosphere of N_2, dichloromethane (5 mL), hydroxybenzotriazole hydrate (170 mg, 1.11 mmol), cyclohexanecarboxylic acid (187 mg, 1.47 mmol, *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (226 mg, 1.10 mmol), and ethyldiisopropylamine (0.1 mL) were added to the white residue at 0 °C. The cooling bath was removed and the mixture was stirred for 14 h. The reaction mixture was added to a separatory funnel containing $NaHCO_3$ (10 mL), the organic layer was separated, and the aqueous layer was extracted with dichloromethane (10 mL). The combined organic were concentrated and purified via column chromatography (SiO_2, 1:1:18 to 1:1:3

dichloromethane/ethyl acetate/hexanes, gradient elution) to give the title compound **4.29a** (198 mg, 0.28 mmol, 77% yield) as a light yellow oil.

R_f (SiO_2, dichloromethane:ethyl acetate: hexanes = 1: 2: 2) = 0.80.

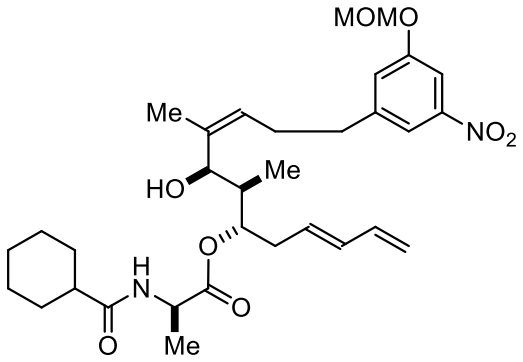
$[\alpha]_{23}^{D}$= 41 (c = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (t, *J* = 1.9, 2H), 7.17 (d, *J* = 8.6, 2H), 7.14 (s, 1H), 6.85 (d, *J* = 8.6, 2H), 6.22 (dt, *J* = 16.9, 10.3, 1H), 5.99 (dd, *J* = 15.6, 9.5, 2H), 5.49 (dt, *J* = 15.8, 7.4, 2H), 5.19 (s, 2H), 5.07 (d, *J* = 17.0, 1H), 4.97 (d, *J* = 10.2, 1H), 4.88 (ddd, *J* = 9.0, 5.7, 3.1, 1H), 4.50 (quintet, *J* = 7.2, 1H), 4.23 (d, *J* = 11.2, 1H), 3.96 (t, *J* = 9.5, 2H), 3.79 (s, 3H), 3.47 (s, 3H), 2.72 (t, *J* = 7.0, 2H), 2.49-2.39 (m, 1H), 2.33-2.18 (m, 3H), 2.10-2.02 (m, 2H), 1.82 (m, 3H), 1.77 (s, 3H), 1.74 (m, 1H), 1.68-1.63 (m, 2H), 1.40 (dt, *J* = 12.1, 6.0, 3H), 1.29 (d, *J* = 7.1, 3H), 1.25-1.18 (m, 2H), 1.01 (d, *J* = 6.8, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 175.5, 173.0, 159.2, 157.7, 149.3, 144.8, 136.6, 135.4, 134.1, 130.7, 129.5, 129.3, 128.7, 123.1, 116.9, 116.3, 113.8, 108.9, 94.7, 75.3, 69.9, 56.4, 55.4, 48.0, 45.4, 39.9, 36.1, 33.7, 29.7, 29.6, 29.2, 26.1, 25.8, 25.8, 25.7, 19.1, 19.0, 11.2 ppm.

FTIR (Neat): λ^{-1} = 2930, 2854, 1737, 1616, 1584, 1531, 1514, 1449, 1349, 1250, 1214, 1150, 1031, 1005 cm^{-1}.

MS (ESI): Calcd. for $C_{40}H_{54}N_2O_9$ (M+ Na^+): 729.4; Found:729.5.



(*R*)-(3*E*,6*S*,7*R*,8*R*,9*Z*)-8-hydroxy-12-(3-(methoxymethoxy)-5-nitrophenyl)-7,9-dimethyldodeca-1,3,9-trien-6-yl 2-(cyclohexanecarboxamido)propanoate (4.37a)

Compound **4.29a** (250 mg, 0.35 mmol), dichloromethane (20 mL), 1,3-dimethoxybenzene (240 mg, 1.77 mmol), and dimethyl sulfide (650 mg. 10.6 mmol), were combined under N_2, cooled to 0°C, and freshly prepared magnesium bromide diethyl etherate (457 mg, 1.77 mmol) was added The cooling bath was removed, and the resulting mixture was stirred for 6 h at ambient temperature. NH_4Cl (10 mL) and ethyl acetate (20 mL) were added to the reaction mixture. The organic layer was separated, washed with brine (5 mL), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified via column chromatography (SiO_2, 1:1:8 to 1:1:3 dichloromethane/ethyl acetate/hexanes, gradient elution) to give the title compound **4.37a** (107 mg, 0.30 mmol, 85% yield) as a light yellow oil.

R_f = (SiO_2, dichloromethane:ethyl acetate: hexanes = 1: 2: 2) = 0.60.

$[\alpha]_{23}^{D}$= 23 (c = 1.0, $CHCl_3$).

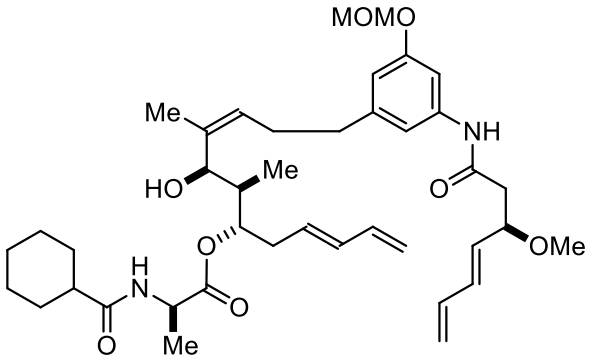
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.17 (t, *J* = 1.8, 1H), 6.23 (dt, *J* = 16.9, 10.3, 1H), 6.04 (dd, *J* = 15.2, 10.5, 1H), 5.91 (d, *J* = 6.8, 1H), 5.54 (ddd, *J* = 15.0, 8.5, 6.2, 1H),

5.25-5.23 (m, 1H), 5.22 (s, 2H), 5.08 (d, *J* = 16.9, 1H), 4.98 (d, *J* = 10.7, 1H), 4.90 (ddd, *J* = 8.8, 7.5, 3.1, 1H), 4.45 (d, *J* = 5.4, 1H), 4.42 (t, *J* = 7.1, 1H), 3.49 (s, 3H), 2.72 (t, *J* = 7.6, 2H), 2.45 (dq, *J* = 14.9, 7.4, 1H), 2.39-2.26 (m, 3H), 2.09 (tt, *J* = 11.7, 3.5, 1H), 1.87-1.82 (m, 3H), 1.76 (s, 3H), 1.66-1.64 (m, 2H), 1.43-1.37 (m, 2H), 1.32 (d, *J* = 7.2, 3H), 1.28-1.20 (m, 5H), 0.97 (d, *J* = 6.9, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 176.1, 173.4, 157.7, 149.3, 145.1, 138.2, 136.7, 134.3, 139.4, 125.6, 122.9, 117.0, 116.3, 109.0, 94.7, 75.6, 70.2, 56.5, 48.4, 45.3, 41.4, 36.0, 34.7, 29.7, 29.6, 29.1, 25.8, 25.8, 25.7, 19.9, 18.3, 10.6 ppm.

FTIR (Neat): λ^{-1} = 3396, 2931, 1734, 1654, 1531, 1450, 1350, 1270, 1214, 1150, 1031, 1005 cm^{-1}.

MS (ESI): Calcd. for $C_{32}H_{46}N_2O_8$ (M+ Na^+): 609.3; Found:609.3.



(*R*)-(3*E*,6*S*,7*R*,8*R*,9*Z*)-8-hydroxy-12-(3-((*R*,*E*)-3-methoxyhepta-4,6-dienamido)-5-(methoxymethoxy)phenyl)-7,9-dimethyldodeca-1,3,9-trien-6-yl 2-(cyclohexanecarboxamido)propanoate (4.38a)

Zinc (1.5 g, 23 mmol) was added in three portions to solution of (*R*)-(3*E*,6*S*,7*R*,8*R*,9*Z*)-8-hydroxy-12-(3-(methoxymethoxy)-5-nitrophenyl)-7,9-dimethyldodeca-1,3,9-trien-6-yl 2-(cyclohexanecarboxamido)propanoate (160 mg, 0.22 mmol), tetrahydrofuran (10 mL. 0.011 M), water (5 mL), methanol (5 mL), and ammonium formate (710 mg, 11 mmol) under argon at 0 °C. The cooling bath was removed and resulting mixture was vigorously stirred at ambient temperature for 14 h. The resulting slurry was decanted into a separatory funnel containing brine (20 mL) and extracted with toluene (3 x 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure (water bath under 30°C). The crude residue was dissolved with dichloromethane (5 mL) under an atmosphere of N_2, and combined with hydroxybenzotriazole hydrate (41 mg, 0.37 mmol) acid **1.64**(40 mg, 0.27 mmol), and ethyldiisopropylamine (0.06 mL, 0.45 mmol). *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (56 mg, 0.30mmol) was added and the solution was stirred at ambient temperature for 18 h. Dichloromethane (10 mL) and

$NaHCO_3$ (5 mL) were added, the organic layer was separated, concentrated under reduced pressure, and purified via column chromatography (SiO_2, 1:1:1 dichloromethane/ethyl acetate/hexanes) to give the title compound **4.38a** (49 mg, 0.071 mmol, 51% yield) as a light yellow oil. The stereochemical assignment was comfirmed by converting the title compound to the known natural product.

R_f (SiO_2, dichloromethane:ethyl ether: Hexanes: Ethyl Acetate = 3: 3: 3: 1) = 0.4.

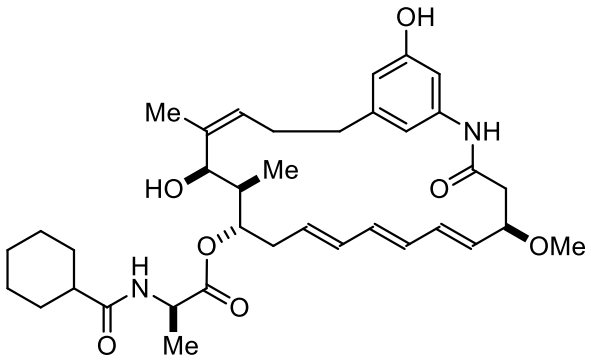
$[\alpha]_{26}^{D}$= 11 (c = 0.95, $CHCl_3$).

^{1}H NMR (400 MHz; $CDCl_3$): δ 8.67 (s, 1H), 7.27 (s, 1H), 6.91 (s, 1H), 6.60 (s, 1H), 6.38-6.16 (m, 6H), 6.03 (dd, *J* = 15.1, 10.5, 1H), 5.61-5.49 (m, 4H), 5.32-5.23 (m, 3H), 5.17-5.12 (m, 4H), 5.08 (d, *J* = 16.7, 1H), 4.98 (d, *J* = 10.2, 1H), 4.90 (ddd, *J* = 8.8, 7.5, 3.1, 2H), 4.52 (quintet, *J* = 7.2, 1H), 4.36 (d, *J* = 5.2, 1H), 4.15-4.13 (m, 1H), 3.47 (s, 3H), 3.33 (s, 3H), 2.67-2.49 (m, 5H), 2.38-2.26 (m, 3H), 2.17-2.08 (m, 3H), 1.87-1.84 (m, 3H), 1.78 (s, 3H), 1.30 (d, *J* = 7.1, 3H), 1.28-1.21 (m, 3H), 0.97 (d, *J* = 6.9, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 173.4, 169.0, 157.7, 144.0, 139.5, 137.4, 136.7, 135.9, 134.2, 134.0, 132.0, 129.4, 126.5, 118.6, 116.2, 113.3, 112.1, 106.0, 94.6, 78.7, 75.8, 69.8, 56.6, 56.2, 48.1, 45.3, 44.0, 42.8, 41.6, 36.1, 34.5, 29.7, 29.6, 25.8, 25.7, 25.7, 19.5, 18.9, 10.5 ppm.

FTIR (Neat): λ^{-1} = 3310, 2930, 1737, 1652, 1604, 1541, 1448, 1374, 1299, 1204, 1146 cm^{-1}.

HRMS (ESI): Calcd. for $C_{40}H_{58}N_2O_8$ (M+ Na^+): 717.40854; Found:717.40808.



(+)-trienomycin A (1.1a)

A solution of compound **4.38a** (7.0 mg, 0.011 mmol) in dichloromethane (11 mL, 0.001 M) was sparged with argon. Bis(tricyclohexylphosphine)-3-phenyl-1H-inden-1-ylideneruthenium(II) dichloride (3.9 mg, 4.2 μmol) was added and the reaction mixture was sparged with argon for 10 min. The resulting mixture was heated at 40 °C for 14 h, cooled to ambient temperature and filtered through a plug of silica gel, eluted with 1:1 ethyl acetate/dichloromethane (50 mL) and discarded fraction, eluted 4:1 ethyl acetate/dichloromethane, collected fraction and concentrated under reduced pressure. The crude residue was dissolved in tetrahydrofuran (3 mL), 3N HCl (3 mL) was added at ambient temperature, and the resulting mixture was allowed to stand for 24 h. The reaction mixture was added dropwise to a solution of 50% $NaHCO_3$ (10 mL), extracted with chloroform (3 x 15 mL), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by reverse-phase HPLC (Agilent Eclipse 5 μm XDB-C18, 9.4 x 250 mm, 63% Methanol in water with 0.1% TFA over 30 min, 2.5 mL/min, RT = 16.1 min.) to give (+)-trienomycin A (**1.1a**) (1.4 mg, .0022 mmol, 21% yield) as a white powder. The spectral data obtained for (+)-trienomycin A were consistent with reported values.[145]

R_f (SiO_2, chloroform/methanol = 9 : 1) = 0.1.

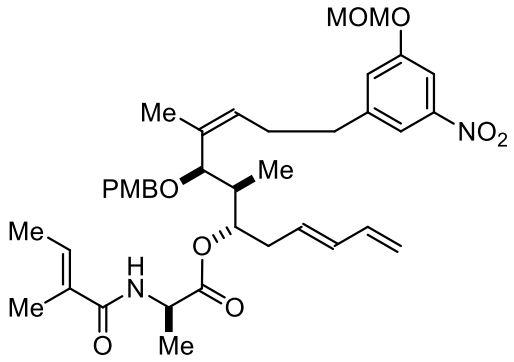
$[\alpha]_{25}^{D}$= 78 (c = 0.014, methanol).

^{1}H NMR (500 MHz, CD_3OD): δ 6.96 (s, 1H), 6.43 (s, 1H), 6.38 (s, 1H), 6.14-6.07 (m, 4H), 5.62-5.55 (m, 2H), 5.21 (s, 1H), 4.62 (s, 1H), 4.27 (q, *J* = 7.3, 1H), 4.06-4.02 (m, 1H), 2.72 (dd, *J* = 12.0, 4.2, 1H), 2.56-2.48 (m, 2H), 2.45-2.37 (m, 2H), 2.31-2.19 (m, 4H), 1.95-1.91 (m, 2H), 1.79-1.76 (m, 2H), 1.74 (s, 3H), 1.75-1.68 (m, 2H), 1.47-1.39 (m, 2H), 1.36 (d, *J* = 7.3, 3H), 1.31-1.17 (m, 4H), 0.90 (d, *J* = 6.8, 3H) ppm.

^{13}C NMR (125 MHz, CD_3OD): δ 179.2, 173.7, 170.9, 158.7, 144.9, 139.8, 135.3, 135.0, 134.7, 132.5, 131.0, 130.6, 125.9, 113.4, 112.8, 107.1, 81.6, 76.4, 69.7, 56.6, 50.0, 45.9, 44.8, 40.3, 374, 33.7, 30.6, 30.5, 26.9, 26.7, 26.7, 20.8, 17.2, 10.1 ppm.

FTIR (Neat): λ^{-1} = 3310, 2930, 1737, 1652, 1604, 1541, 1448, 1374, 1299, 1204, 1146 cm^{-1}.

HRMS (ESI): Calcd. for $C_{36}H_{50}N_2O_7$ ($M+Na^+$): 645.35102; Found:645.35162.



(*R*)-(3*E*,6*S*,7*S*,8*R*,9*Z*)-8-((4-methoxybenzyl)oxy)-12-(3-(methoxymethoxy)-5-nitrophenyl)-7,9-dimethyldodeca-1,3,9-trien-6-yl 2-((*E*)-2-methylbut-2-enamido)propanoate (4.29f)

Compound **4.28** (300 mg, 0.37 mmol) and tetrahydrofuran (10 mL) were combined under N_2. The reaction vessel was cooled to 0 °C and piperidine (5 mL) was added. The reaction vessel was warmed to ambient temperature and stirred for 30 min. The resulting mixture was concentrated under reduced pressure and azeotroped with toluene (3 x 10 mL). Under an atmosphere of N_2, dichloromethane (5 mL), hydroxybenzotriazole hydrate (170 mg, 1.11 mmol), tiglic acid (147 mg, 1.47 mmol, *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (226 mg, 1.10 mmol), and ethyldiisopropylamine (0.1 mL) were added to the white residue at 0 °C. The cooling bath was removed and the mixture was stirred for 14 h. The reaction mixture was added to a separatory funnel containing $NaHCO_3$ (10 mL), the organic layer was separated, and the aqueous layer was extracted with dichloromethane (10 mL). The combined organic were concentrated and purified via column chromatography (SiO_2, 1:1:6 to 1:1:3 dichloromethane/diethyl ether/hexanes, gradient elution) to give the title compound **4.29f** (199 mg, 0.33 mmol, 88% yield) as a light yellow oil.

R_f = (SiO_2, dichloromethane:ethyl acetate: hexanes = 1: 2: 2) = 0.80.

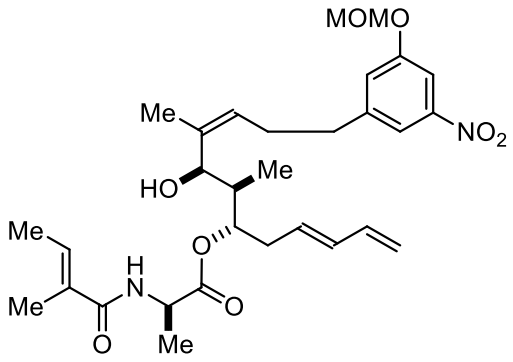
$[\alpha]_{23}^{D}$= +48 (c = 0.95, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.67 (m, 2H), 7.16 (d, *J* = 8.7, 2H), 7.13 (t, *J* = 1.9, 1H), 6.83 (d, *J* = 8.7, 2H), 6.46-6.40 (m, 1H), 6.28 (d, *J* = 7.3, 1H), 6.21 (dt, *J* = 16.9, 10.4, 1H), 5.99 (dd, *J* = 15.2, 10.5, 1H), 5.52-5.45 (m, 2H), 5.17 (s, 2H), 5.05 (d, *J* = 16.8, 1H), 4.96 (d, *J* = 10.3, 1H), 4.87 (ddd, *J* = 9.0, 5.8, 3.1, 1H), 4.54 (quintet, *J* = 7.2, 1H), 4.22 (d, *J* = 11.2, 1H), 3.97-3.93 (m, 2H), 3.76 (s, 3H), 3.45 (s, 3H), 2.73-2.69 (m, 2H), 2.43 (dq, *J* = 15.2, 7.6, 1H), 2.31-2.17 (m, 3H), 2.08-2.03 (m, 1H), 1.81 (s, 3H), 1.76 (s, 3H), 1.72 (dd, *J* = 7.0, 1.0, 3H), 1.32 (d, *J* = 7.1, 3H), 1.01 (d, *J* = 6.9, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 168.5, 159.1, 157.6, 149.2, 144.7, 136.5, 135.3, 134.0, 131.3, 130.6, 129.4, 129.2, 128.7, 123.0, 116.8, 116.2, 113.7, 108.7, 94.5, 77.2, 75.2, 69.7, 56.3, 55.3, 48.3, 39.7, 36.0, 33.5, 29.1, 18.9, 18.7, 13.9, 12.3, 11.2 ppm.

FTIR (Neat): λ^{-1} =2938, 2857,1780, 1736, 1665, 1612, 1532, 1514, 1444, 1373, 1349, 1271, 1244. 1174, 1150, 1032, 1010 cm^{-1}.

HRMS (ESI): Calcd. for $C_{38}H_{50}N_2O_9$ (M+ Na^+): 701.34085; Found: 701.33997.



(*R*)-(3*E*,6*S*,7*R*,8*R*,9*Z*)-8-hydroxy-12-(3-(methoxymethoxy)-5-nitrophenyl)-7,9-dimethyldodeca-1,3,9-trien-6-yl 2-((*E*)-2-methylbut-2-enamido)propanoate (4.37f)

Freshly prepared magnesium bromide diethyl etherate (260 mg, 3.0 mmol), dichloromethane (40 mL), 1,3-dimethoxybenzene (200 mg, 1.5 mmol), and dimethyl sulfide (600 mg. 8.9 mmol), were combined under N_2 and cooled to 0 °C. A solution of compound **4.29f** (200 mg, 0.30 mmol) and dichloromethane (10 mL) was added, the cooling bath was removed the resulting mixture was stirred for 1.5 h at ambient temperature. The reaction vessel was cooled −78 °C, and tetrahydrofuran (20 mL) was added followed by 50% $NaHCO_3$ (10 mL). The resulting mixture was warmed to ambient temperature, and extracted with chloroform (3 x 30 mL). The organic extracts were combined, dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified via column chromatography (SiO_2, 1:1:2 to 1:2:2 dichloromethane/ethyl acetate/hexanes, gradient elution) to give the title compound **4.37f** (115 mg, 0.21 mmol, 70% yield) as a light yellow oil.

$\underline{R_f}$ = (SiO_2, dichloromethane:ethyl acetate: hexanes = 1: 2: 2) = 0.50.

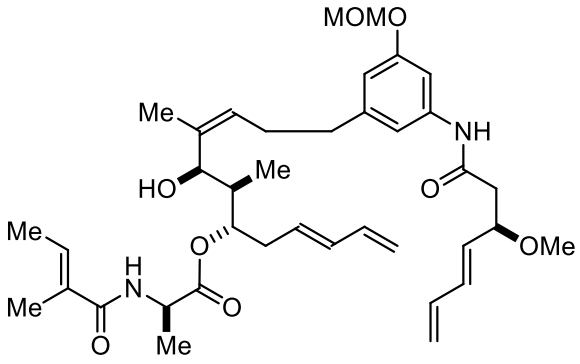
$[\alpha]_{24}^{D}$= 30 (c = 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (s, 2H), 7.16 (s, 1H), 6.46 (q, *J* = 6.9, 1H), 6.27-6.18 (m, 2H), 6.27-6.18 (m, 2H), 6.04 (dd, *J* = 15.0, 10.5, 1H), 5.54 (dt, *J* = 14.8, 7.4, 1H), 5.25-5.21 (m, 3H), 5.08 (d, *J* = 16.9, 1H), 4.97 (d, *J* = 10.1, 1H), 4.90 (td, *J* = 8.0, 2.6, 1H), 4.49-4.42 (m, 2H), 3.50 (s, 3H), 2.71 (t, *J* = 7.6, 2H), 2.50-2.25 (m, 5H), 1.89-1.85 (m, 1H), 1.82 (s, 3H), 1.76 (s, 3H), 1.73 (d, *J* = 7.0, 3H), 1.35 (d, *J* = 7.2, 3H), 0.96 (d, *J* = 6.8, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.4, 169.1, 157.6, 149.2, 145.1, 138.2, 136.6, 134.3, 131.9, 131.1, 129.3, 125.5, 122.9, 116.9, 116.3, 108.9, 94.6, 75.5, 70.2, 56.4, 48.7, 41.3, 35.9, 34.6, 29.0, 19.8, 18.3, 14.1, 12.3, 10.6 ppm.

FTIR (Neat): λ^{-1} = 3359, 2929, 1723, 1661, 1528, 1451, 1350, 1288, cm^{-1}.

HRMS (ESI): Calcd. for $C_{30}H_{42}N_2O_8$ (M+ Na^+): 581.28334; Found: 581.28427.



(*R*)-(3*E*,6*S*,7*R*,8*R*,9*Z*)-8-hydroxy-12-(3-((*R*,*E*)-3-methoxyhepta-4,6-dienamido)-5-(methoxymethoxy)phenyl)-7,9-dimethyldodeca-1,3,9-trien-6-yl 2-((*E*)-2-methylbut-2-enamido)propanoate (4.38f)

Zinc (1.2 g, 18 mmol) was added to solution of (*R*)-(3*E*,6*S*,7*R*,8*R*,9*Z*)-8-hydroxy-12-(3-(methoxymethoxy)-5-nitrophenyl)-7,9-dimethyldodeca-1,3,9-trien-6-yl 2-((*E*)-2-methylbut-2-enamido)propanoate **4.37f** (100 mg, 0.18 mmol), tetrahydrofuran (10 mL), water (5 mL), methanol (5 mL), and ammonium formate (560 mg, 9.0 mmol) under argon at 0 °C. The cooling bath was removed and the resulting mixture was vigorously stirred at ambient temperature for 14 h. The resulting slurry was decanted into a separaory funnel containing brine (20 mL) and extracted with toluene (3 x 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure (water bath under 30°C). The crude residue was dissolved with dichloromethane (5 mL) under an atmosphere of N_2, and combined with hydroxybenzotriazole hydrate (56 mg, 0.37 mmol), acid **1.64** (58 mg, 0.37 mmol), and ethyldiisopropylamine (0.1 mL, 0.72 mmol). *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (226 mg, 1.10 mmol) was added and the solution was stirred at ambient temperature for 18 h. Dichloromethane (10 mL) and

$NaHCO_3$ (5 mL) were added, the organic layer was separated, concentrated under reduced pressure, and purified via column chromatography (SiO_2, 1:1:1 dichloromethane/ethyl acetate/hexanes) to give the title compound **4.38f** (69 mg, 0.10 mmol, 58% yield) as a light yellow oil. The stereochemical assignment was comfirmed by converting the title compound to the known natural product.

R_f (SiO_2, hexanes/EtOAc/DCM = 1:1:1) = 0.34.

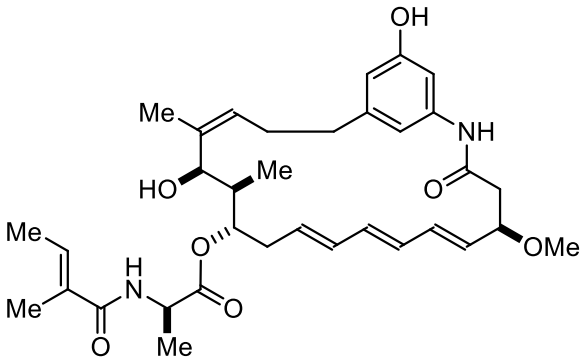
$[\alpha]_{24}^{D}$= +16 (c = 0.90, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): 8.72 (s, 1H), 7.29 (t, *J* = 1.7, 1H), 6.91 (s, 1H), 6.59 (s, 1H), 6.50 (q, *J* = 6.7, 1H), 6.43 (d, *J* = 7.1, 1H), 6.38-6.19 (m, 3H), 6.04 (dd, *J* = 15.1, 10.5, 1H), 5.59-5.49 (m, 2H), 5.27-5.23 (m, 2H), 5.18-5.12 (m, 3H), 5.08 (d, *J* = 17.0, 2H), 4.96 (d, *J* = 10.2, 1H), 4.92 (td, *J* = 8.2, 2.4, 1H), 4.59 (dt, *J* = 14.3, 7.1, 2H), 4.36 (d, *J* = 5.1, 1H), 4.12 (td, *J* = 7.9, 4.2, 1H), 3.47 (s, 3H), 3.32 (s, 3H), 2.65-2.48 (m, 4H), 2.40-2.24 (m, 3H), 2.24-2.17 (m, 2H), 1.84 (s, 3H), 1.77 (s, 3H), 1.75 (d, *J* = 7.0, 3H), 1.34 (d, *J* = 7.1, 3H), 0.97 (d, *J* = 6.9, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5, 169.0, 168.8, 157.7, 144.0, 139.6, 137.4, 136.7, 136.0, 134.3, 133.9, 132.1, 131.2, 129.4, 126.4, 119.6, 116.2, 113.3, 112.1, 106.0, 94.6, 78.8, 75.9, 69.8, 56.6, 56.2, 48.6, 44.0, 42.8, 41.6, 36.1, 34.5, 29.6, 19.5, 18.9, 14.1, 12.4, 10.5 ppm.

FTIR (Neat): λ^{-1} = 3332, 2970, 2935, 1736, 1663, 1616, 1557, 1437, 1378, 1207, 1147cm^{-1}.

HRMS (ESI): Calcd. for $C_{38}H_{54}N_2O_8$ ($M+Na^+$): 689.37724; Found: 689.37732.



(+)-trienomycin F (1.1f)

A solution of **4.38f** (7.0 mg, 0.011 mmol) in dichloromethane (11 mL, 0.001 M) was sparged with argon. Bis(tricyclohexylphosphine)-3-phenyl-1H-inden-1-ylideneruthenium(II) dichloride (3.9 mg, 4.2 μmol) was added and the reaction mixture was sparged with argon for 10 min. The resulting mixture was heated at 40 °C for 14 h, cooled to ambient temperature and filtered through a plug of silica gel, eluted with 1:1 ethyl acetate/dichloromethane (50 mL) and discarded the fraction, eluted 4:1 ethyl acetate/dichloromethane, collected fraction and concentrated under reduced pressure. The crude residue was dissolved in tetrahydrofuran (2 mL), 3N HCl (2 mL) was added at ambient temperature, and the resulting mixture was allowed to stand for 24 h. The reaction mixture was added dropwise to a solution of 50% $NaHCO_3$ (10 mL), extracted with chloroform (3 x 15 mL), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by reverse-phase HPLC (Agilent Eclipse 5 μm XDB-C18, 9.4 x 250 mm, 60% Methanol in water with 0.1% TFA over 30 min, 2.4 mL/min, RT = 16.3 min.) to give (+)-trienomycin F (1.6 mg, 0.0026 mmol, 24%

yield) as a white powder. The spectral data obtained for (+)-trienomycin F (**1.1f**) were consistent with reported values.[25]

R_f (SiO_2, $CHCl_3$/MEOH =9 : 1) = 0.1.

$[\alpha]_{24}^{D}$= 123 (c = 0.016, $CHCl_3$).

^{1}H NMR (600 MHz; $CDCl_3$): δ 7.46 (t, *J* = 1.9, 1H), 7.43 (s, 1H), 6.92 (br s, 1H), 6.52 (qd, *J* = 6.9, 1.3, 1H), 6.45 (s, 1H), 6.26-6.21 (m, 3H), 6.08-6.06 (m, 2H), 6.02-5.99 (m, 1H), 5.59 (dd, *J* = 15.6, 6.4, 1H), 5.58-5.52 (m, 1H), 5.19-5.17 (m, 1H), 4.91 (ddd, *J* = 9.4, 5.7, 2.3, 1H), 4.60 (br s, 1H), 4.45 (quintet, *J* = 7.0, 1H), 4.12-4.09 (m, 1H), 3.38 (s, 3H), 2.73 (dd, *J* = 13.9, 3.7, 1H), 2.68-2.61 (m, 1H), 2.58 (dd, *J* = 13.9, 8.3, 1H), 2.51-2.42 (m, 4H), 2.32 (ddd, *J* = 14.5, 8.7, 1.5, 1H), 2.19-2.13 (m, 1H), 1.99-1.93 (m, 1H), 1.82 (t, *J* = 1.2, 3H), 1.78 (s, 3H), 1.74 (dd, *J* = 6.9, 0.9, 3H), 1.35 (d, *J* = 7.1, 3H), 0.90 (d, *J* = 6.9, 3H) ppm.

^{13}C NMR (150 MHz, CDCl3): δ 172.9, 169.3, 168.5, 157.1, 144.0, 138.6, 138.3, 134.1, 133.4, 133.3, 132.7, 130.6, 130.5, 129.4, 129.1, 124.5, 111.8, 110.8, 105.7, 78.5, 75.4, 68.4, 56.8, 48.8, 43.5, 39.6, 36.2, 33.1, 29.6, 20.3, 17.8, 14.0, 12.1, 9.8 ppm.

FTIR (Neat): λ^{-1} = 3310, 2930, 1737, 1652, 1604, 1541, 1448, 1374, 1299, 1204, 1146 cm^{-1}.

HRMS (ESI): Calcd. for $C_{34}H_{46}N_2O_7$ (M-H)-: 593.32322; Found: 593.32344.

4.6 Spectra relevant to chapter 4

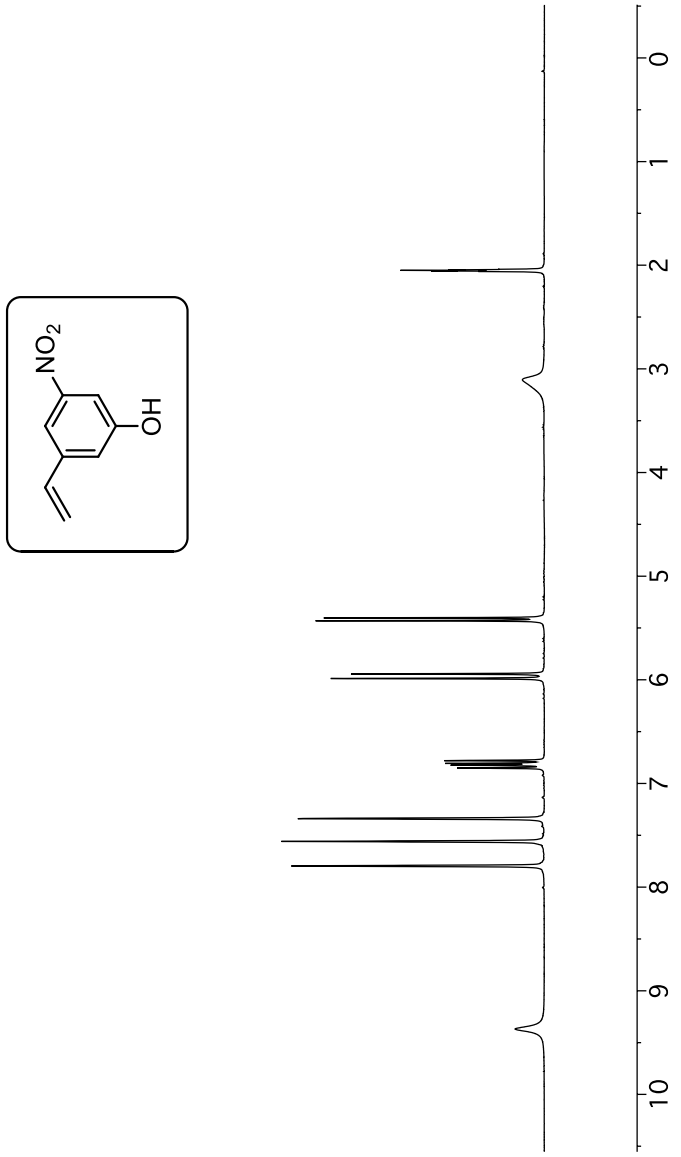


Figure 4.1 ^{1}H NMR spectrum of compound **4.4**

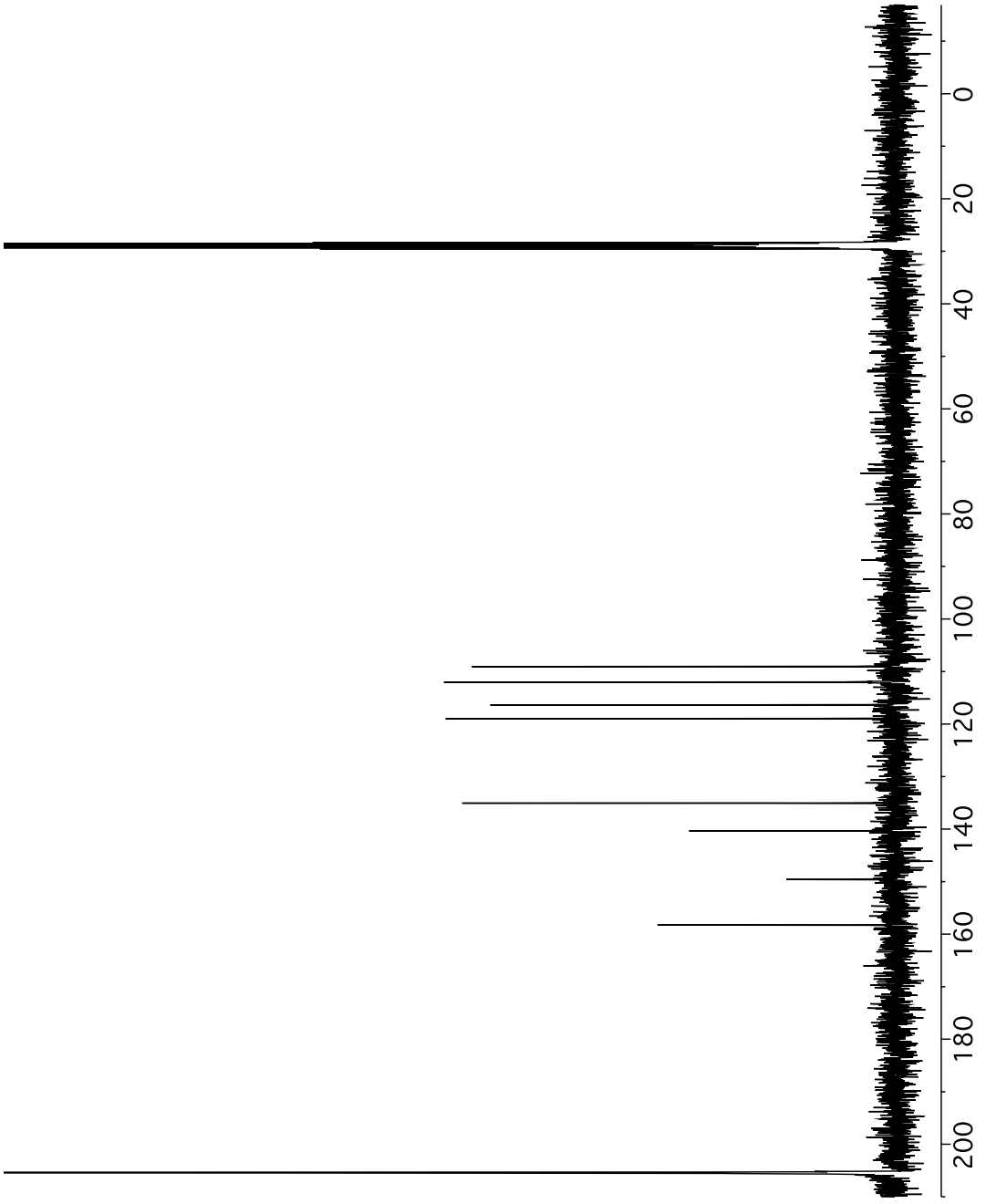


Figure 4.2 ^{13}C NMR spectrum of compound **4.4**

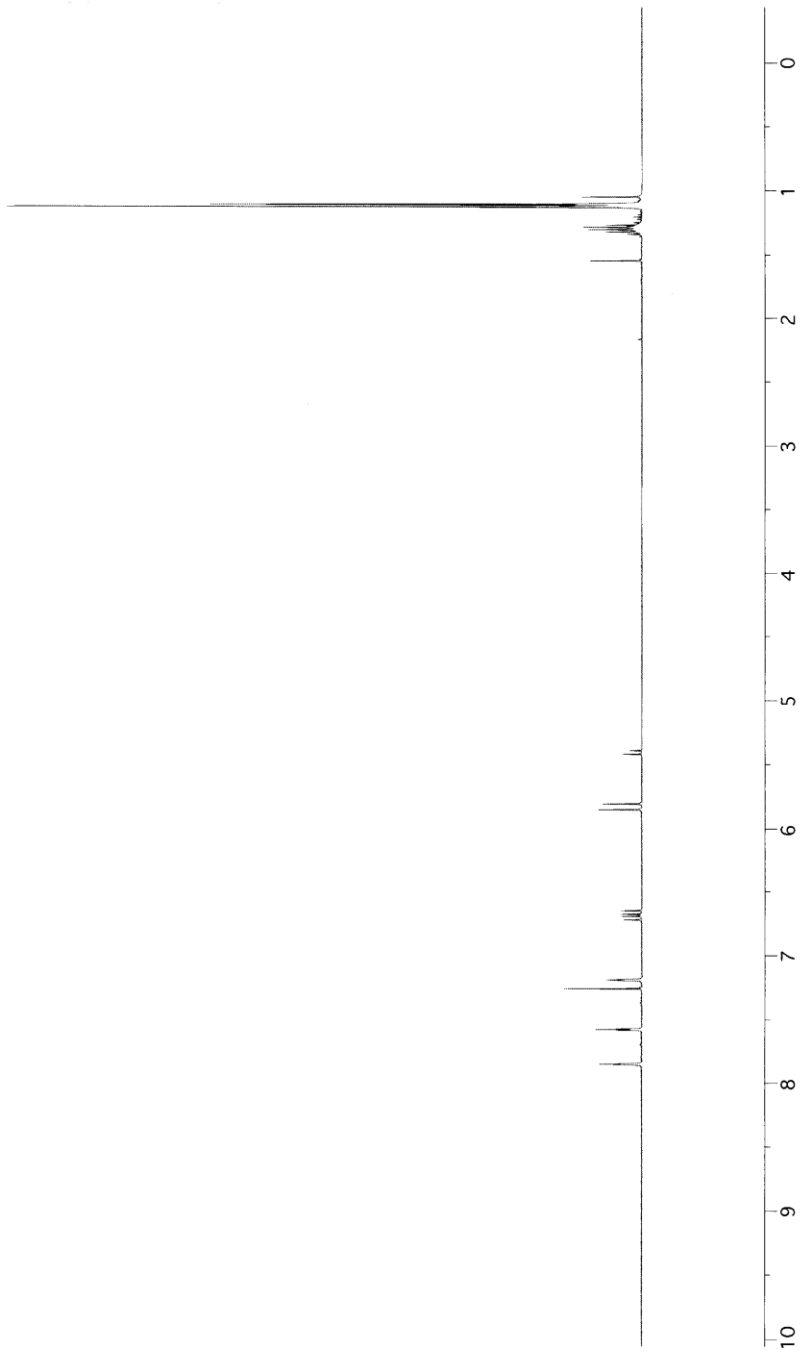


Figure 4.3 ^{1}H NMR spectrum of compound **4.13**

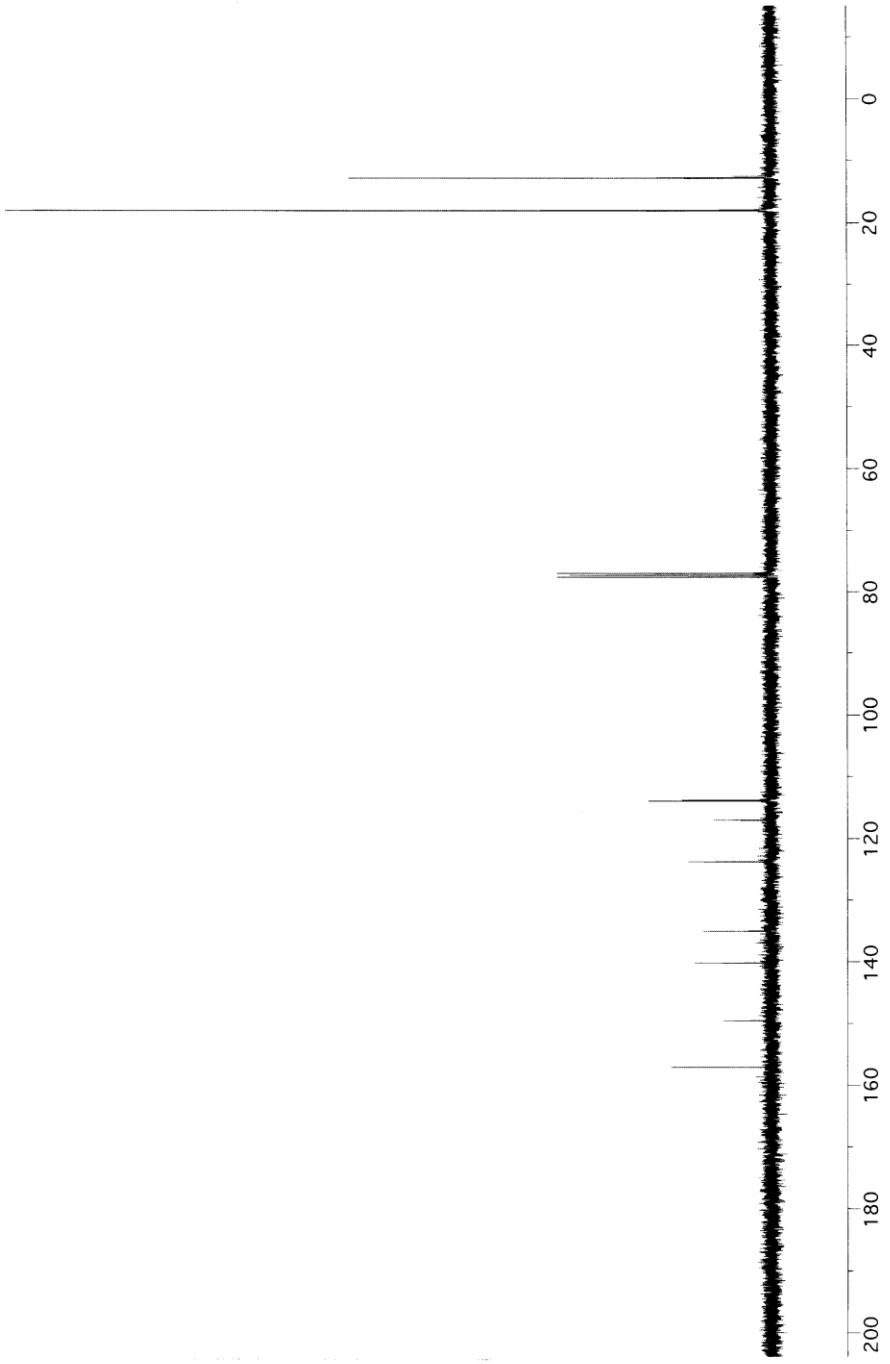


Figure 4.4 ^{13}C NMR spectrum of compound **4.13**

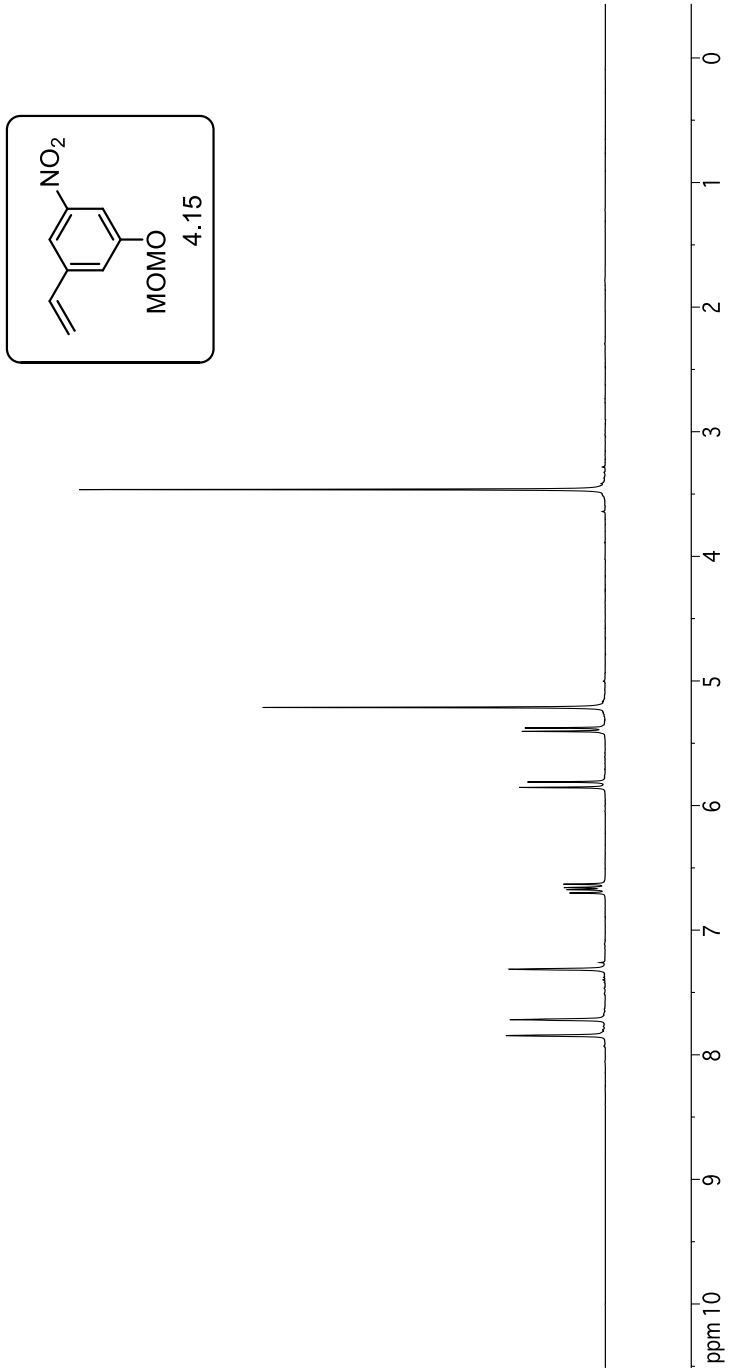


Figure 4.5 ^{1}H NMR spectrum of compound **4.15**

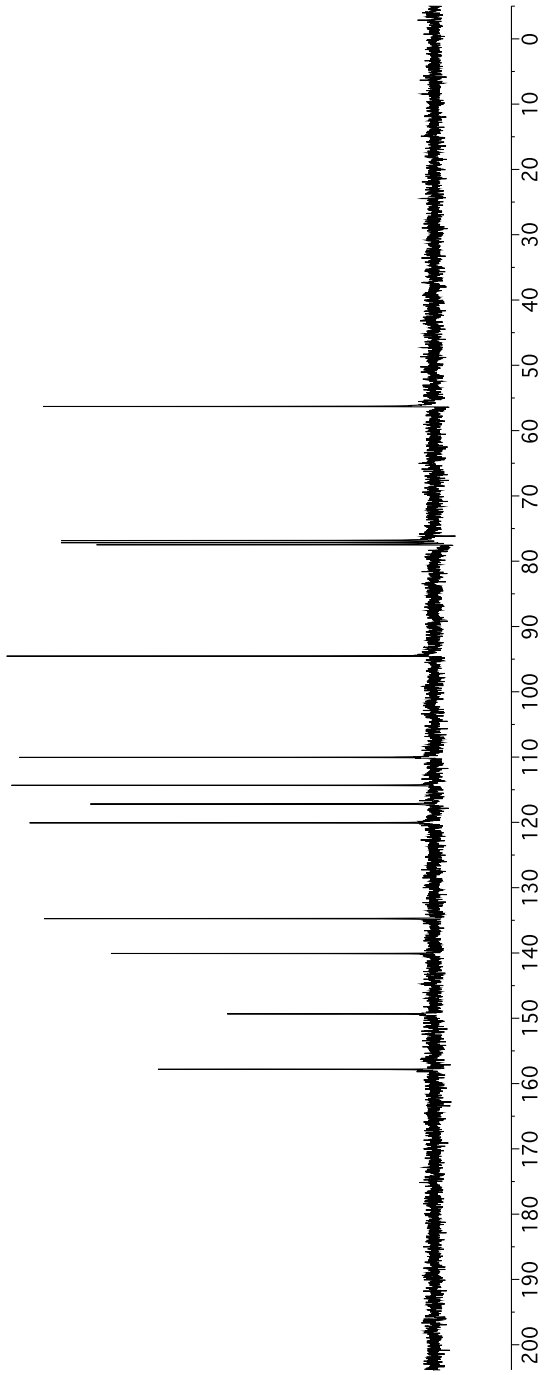


Figure 4.6 ^{13}C NMR spectrum of compound **4.15**

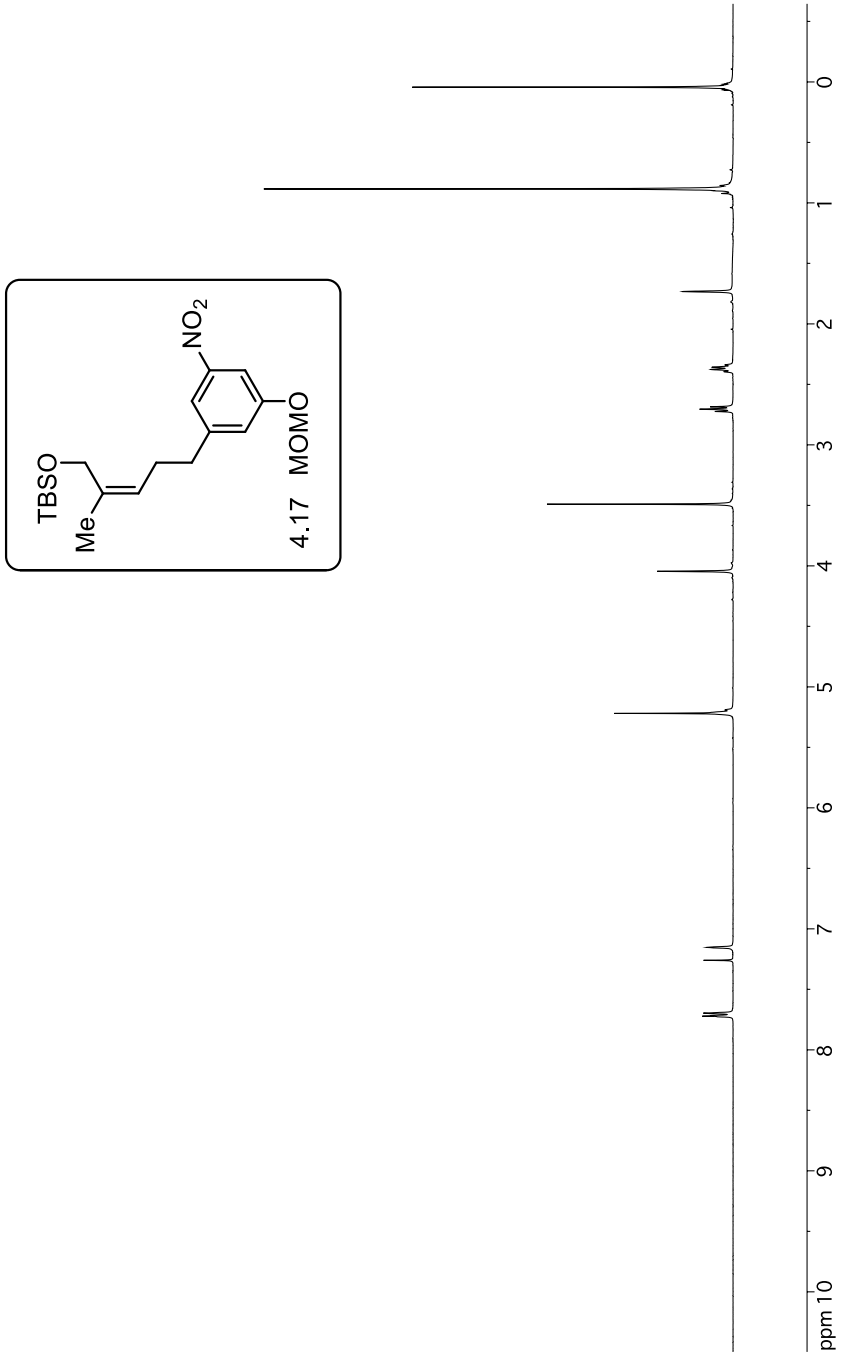


Figure 4.7 ^{1}H NMR spectrum of compound **4.17**

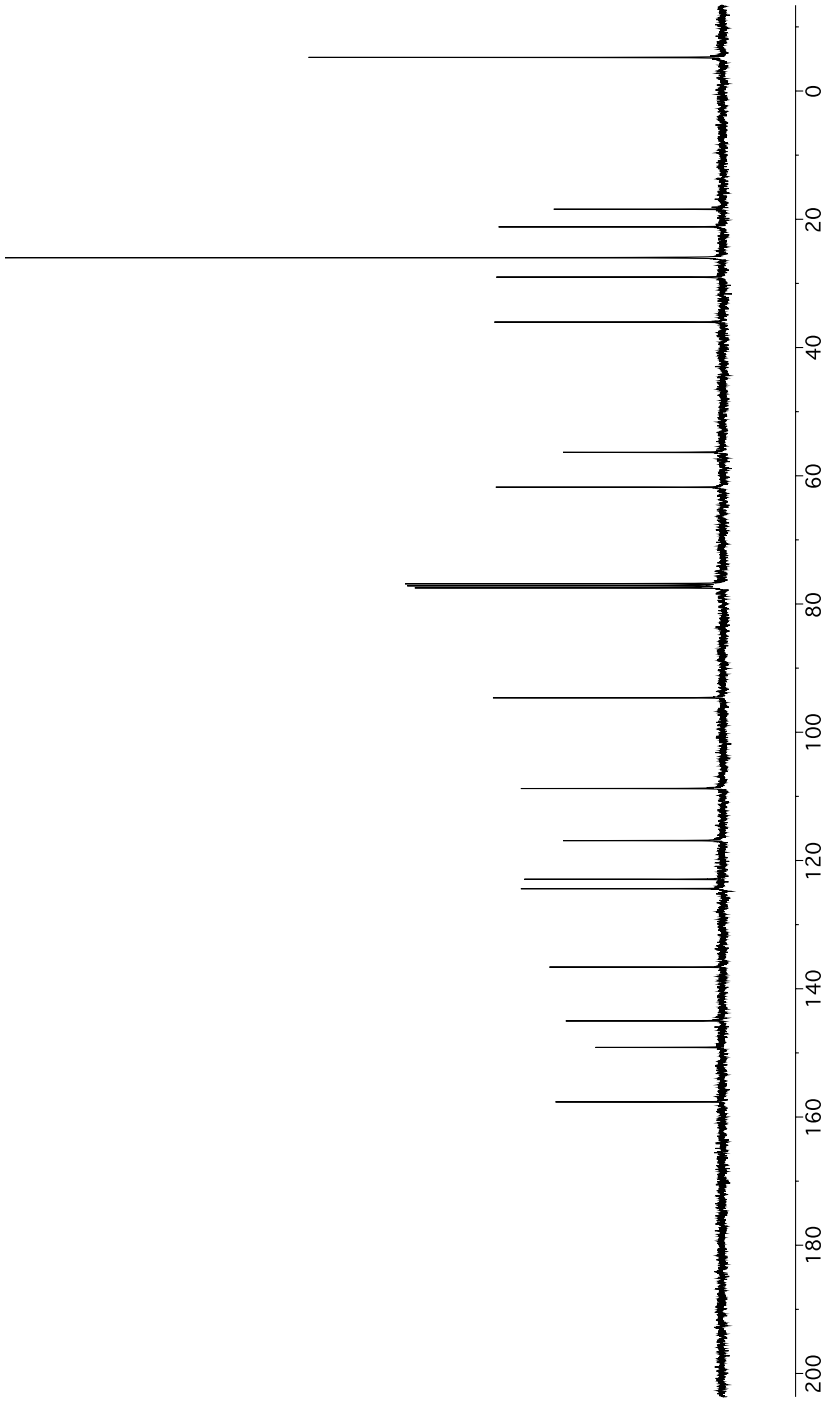


Figure 4.8 ^{13}C NMR spectrum of compound **4.17**

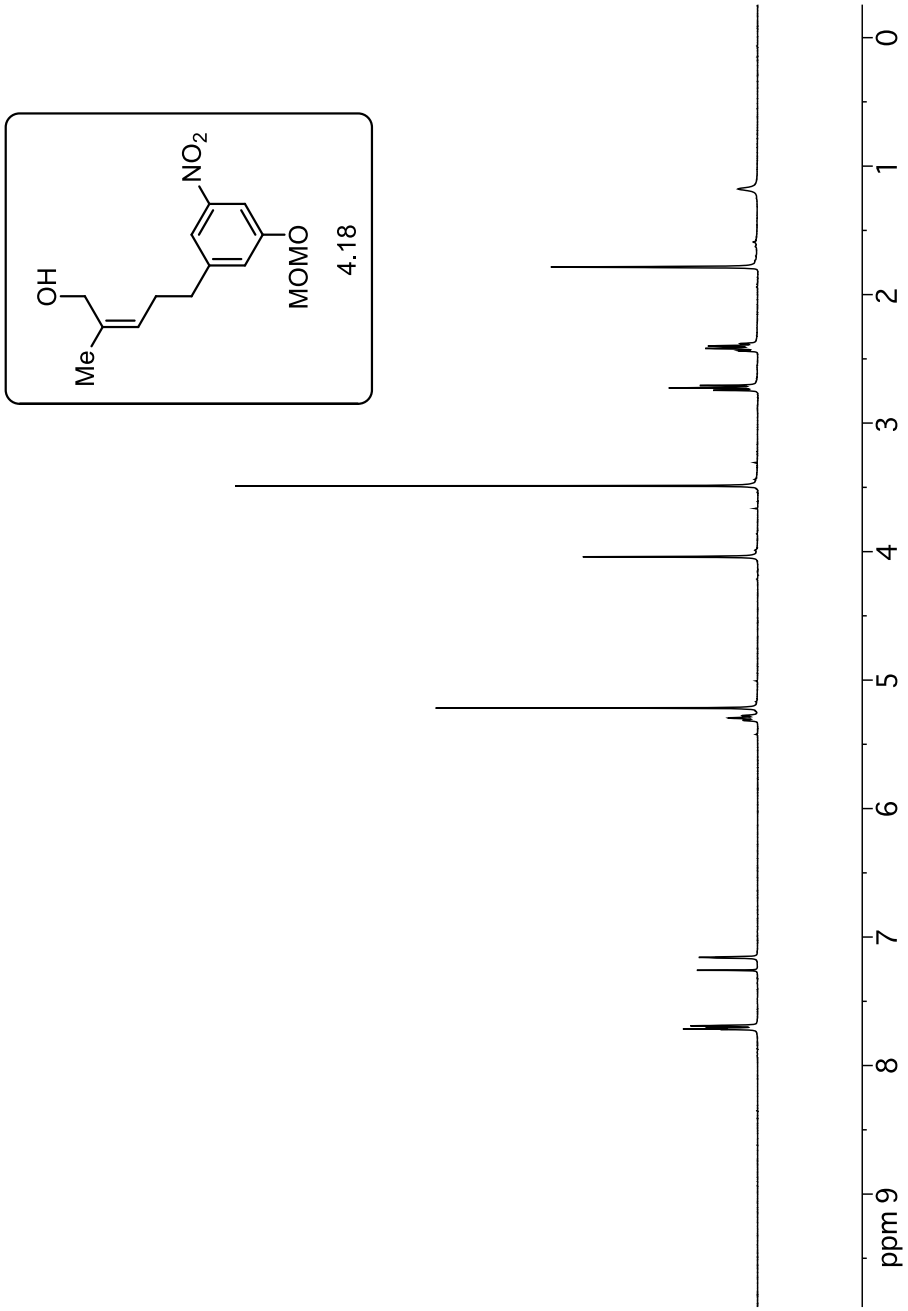


Figure 4.9 ^{1}H NMR spectrum of compound **4.18**

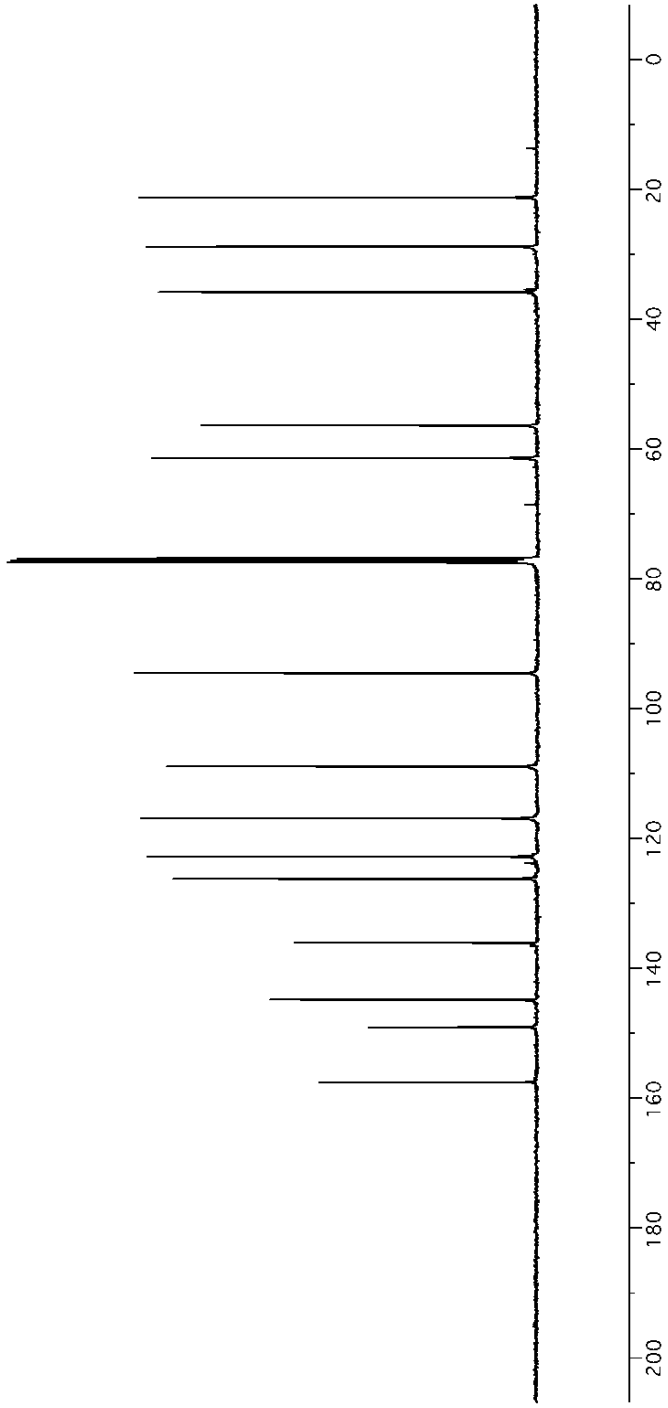


Figure 4.10 ^{13}C NMR spectrum of compound **4.18**

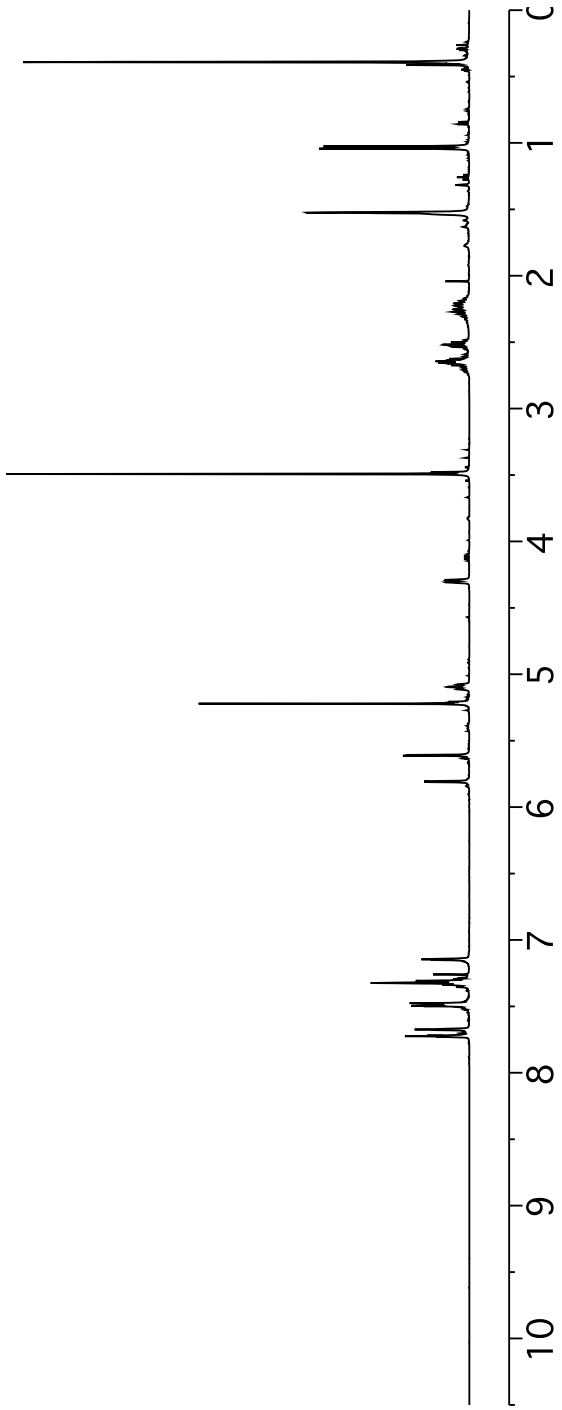


Figure 4.11 ^{1}H NMR spectrum of compound **4.19**

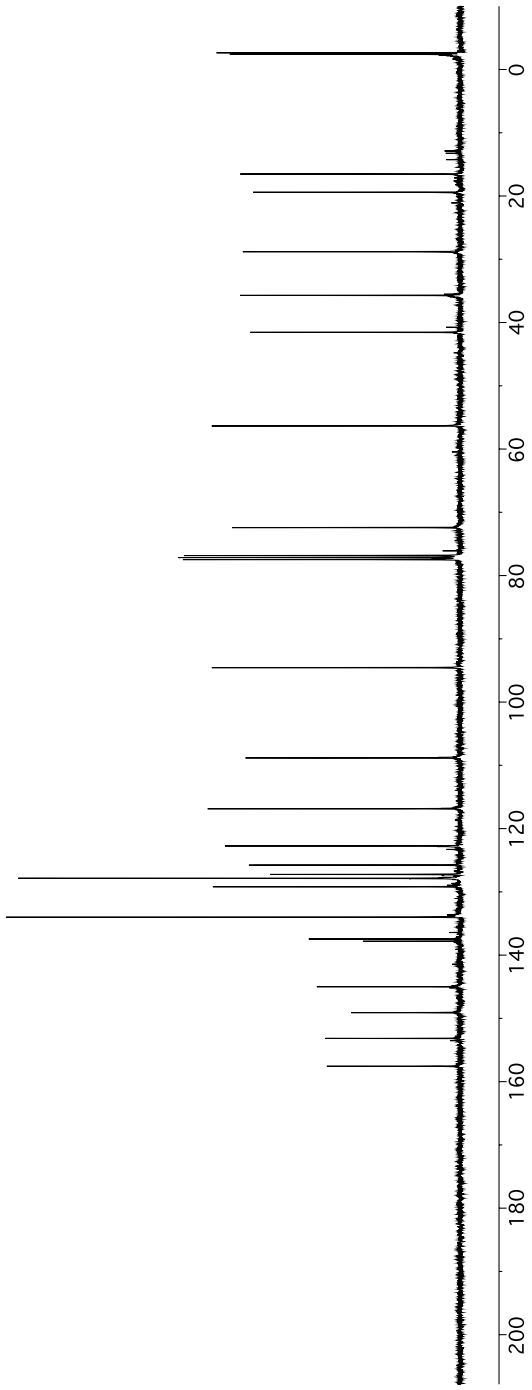


Figure 4.12 ^{13}C NMR spectrum of compound **4.19**

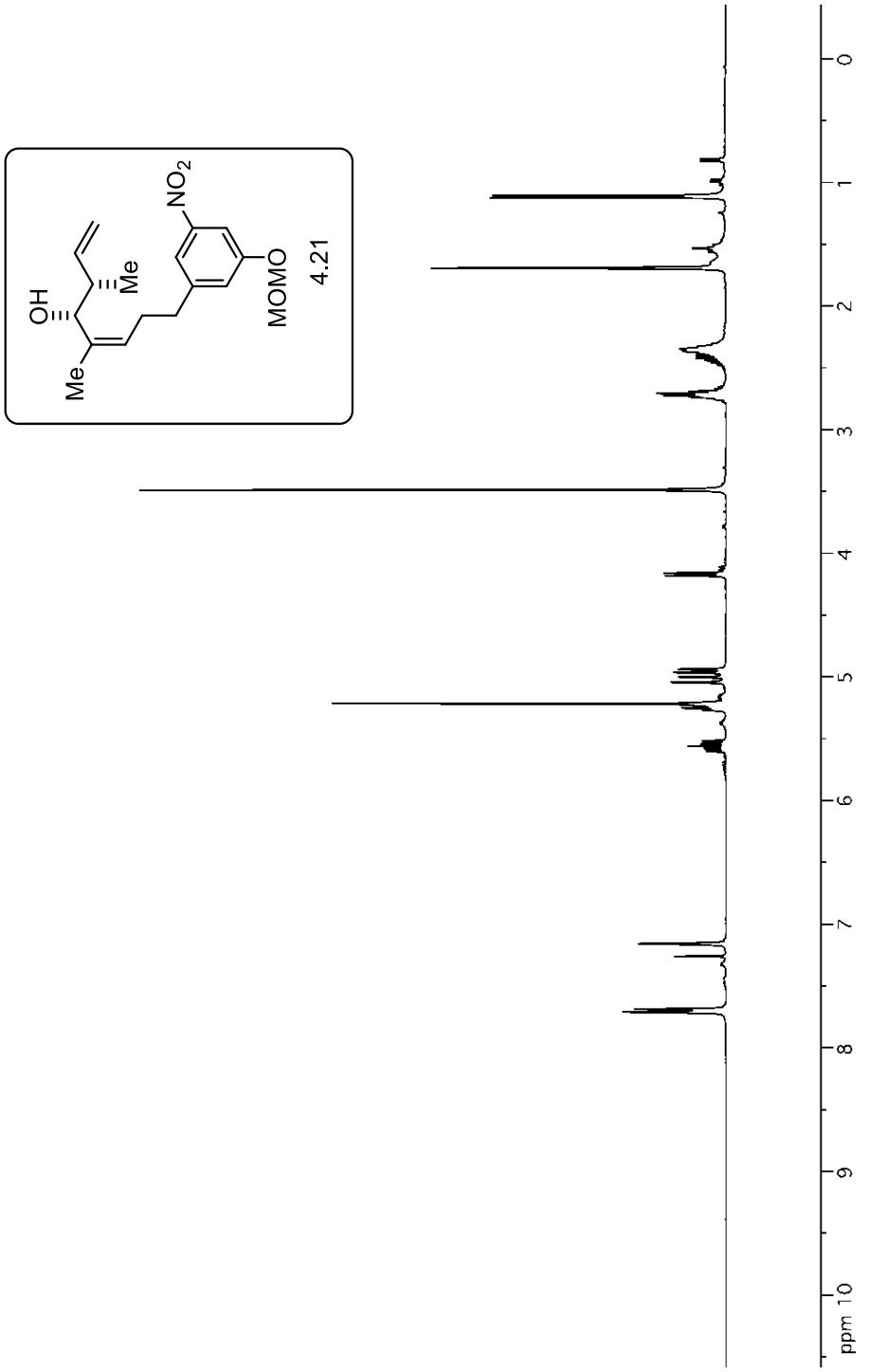


Figure 4.13 ^{1}H NMR spectrum of compound **4.21**

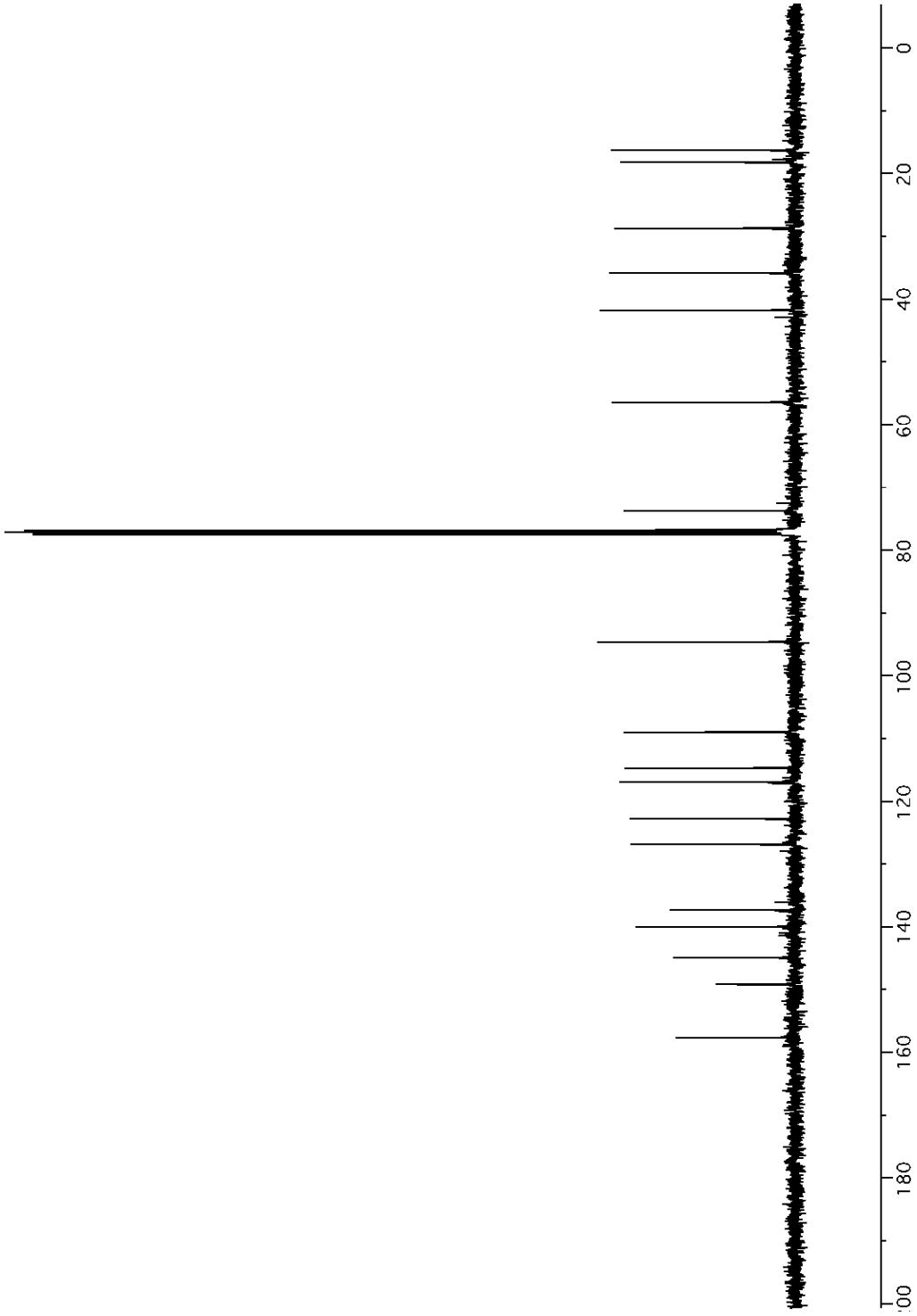


Figure 4.14 ^{13}C NMR spectrum of compound **4.21**

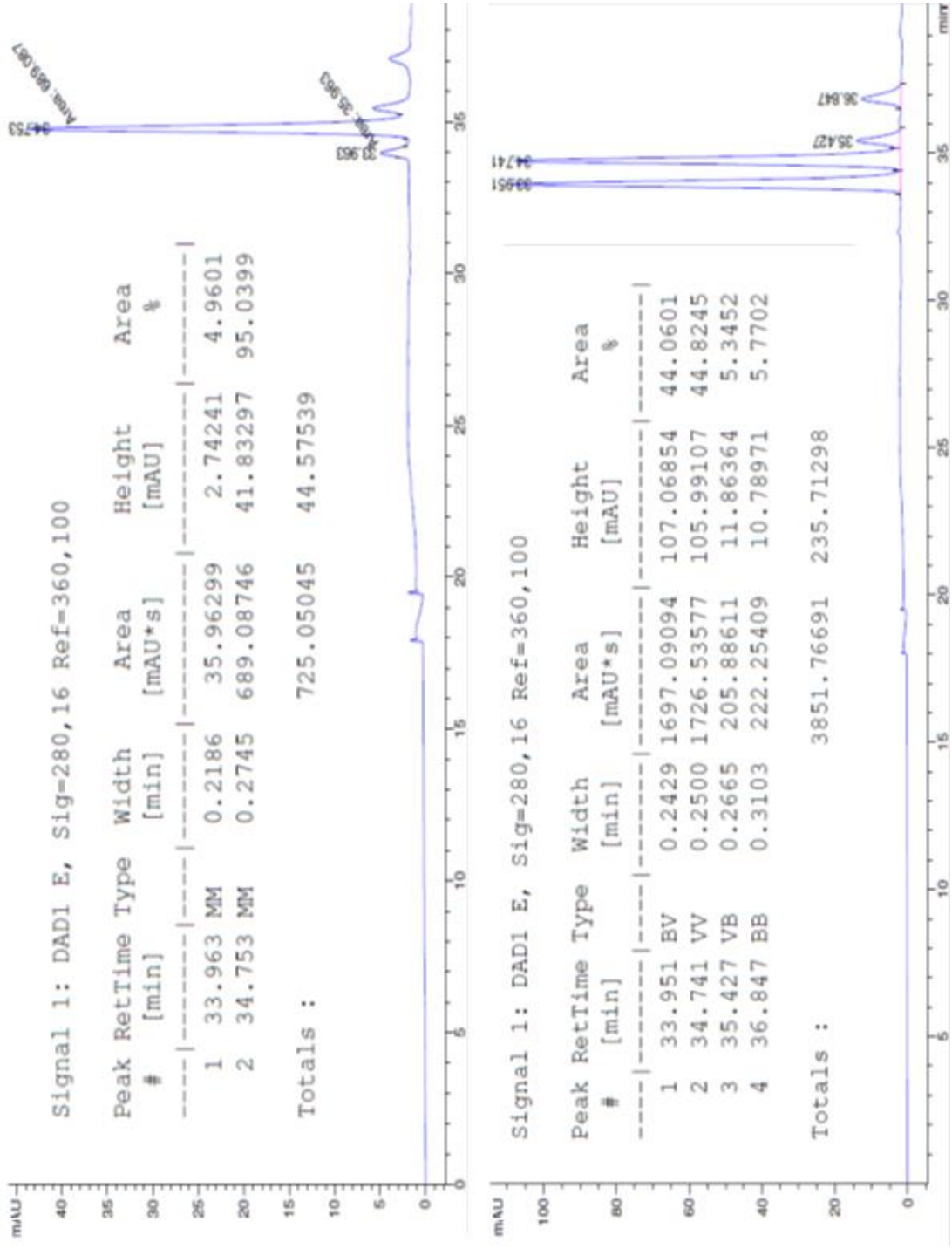


Figure 4.15 HPLC data for compound **4.21**

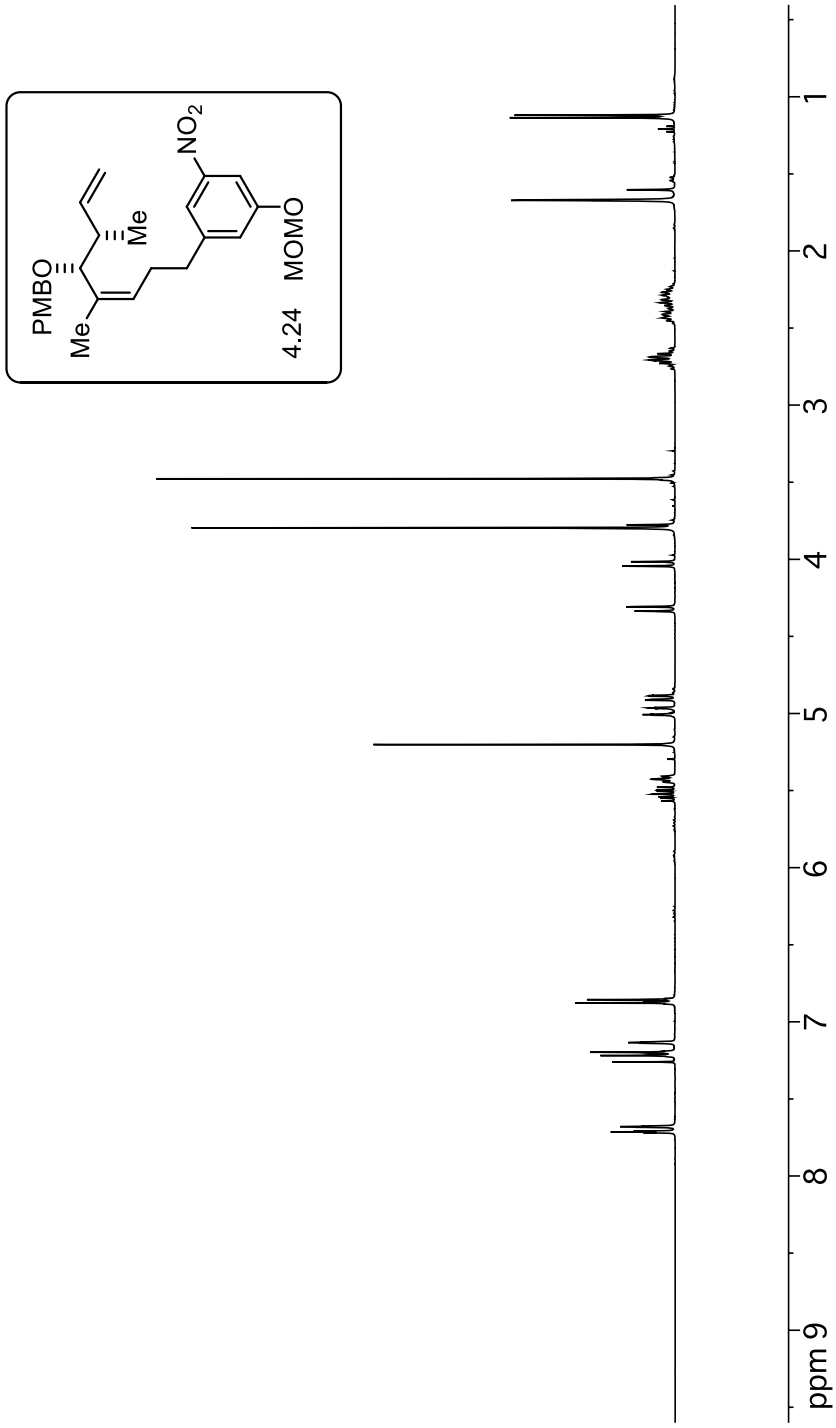


Figure 4.16 ^{1}H NMR spectrum of compound **4.24**

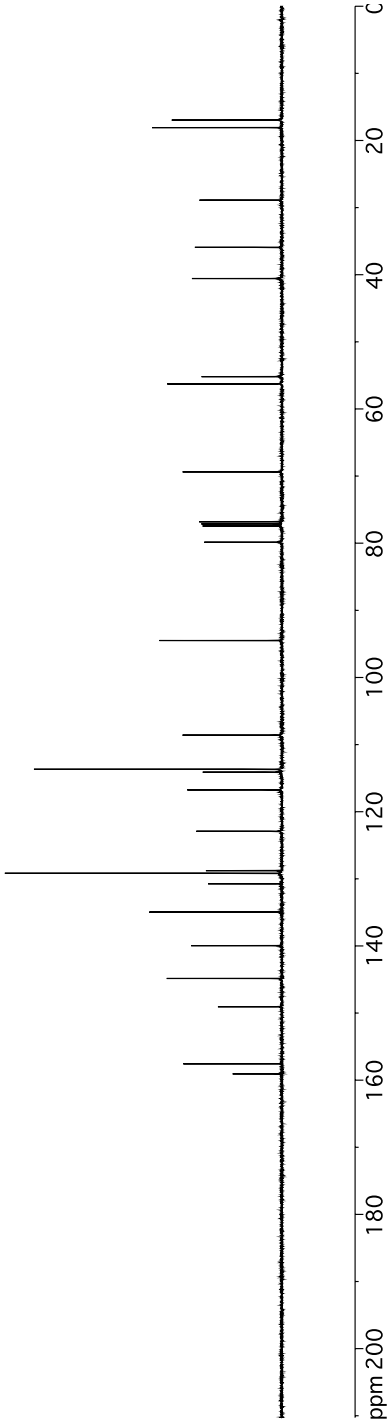


Figure 4.17 ^{13}C NMR spectrum of compound **4.24**

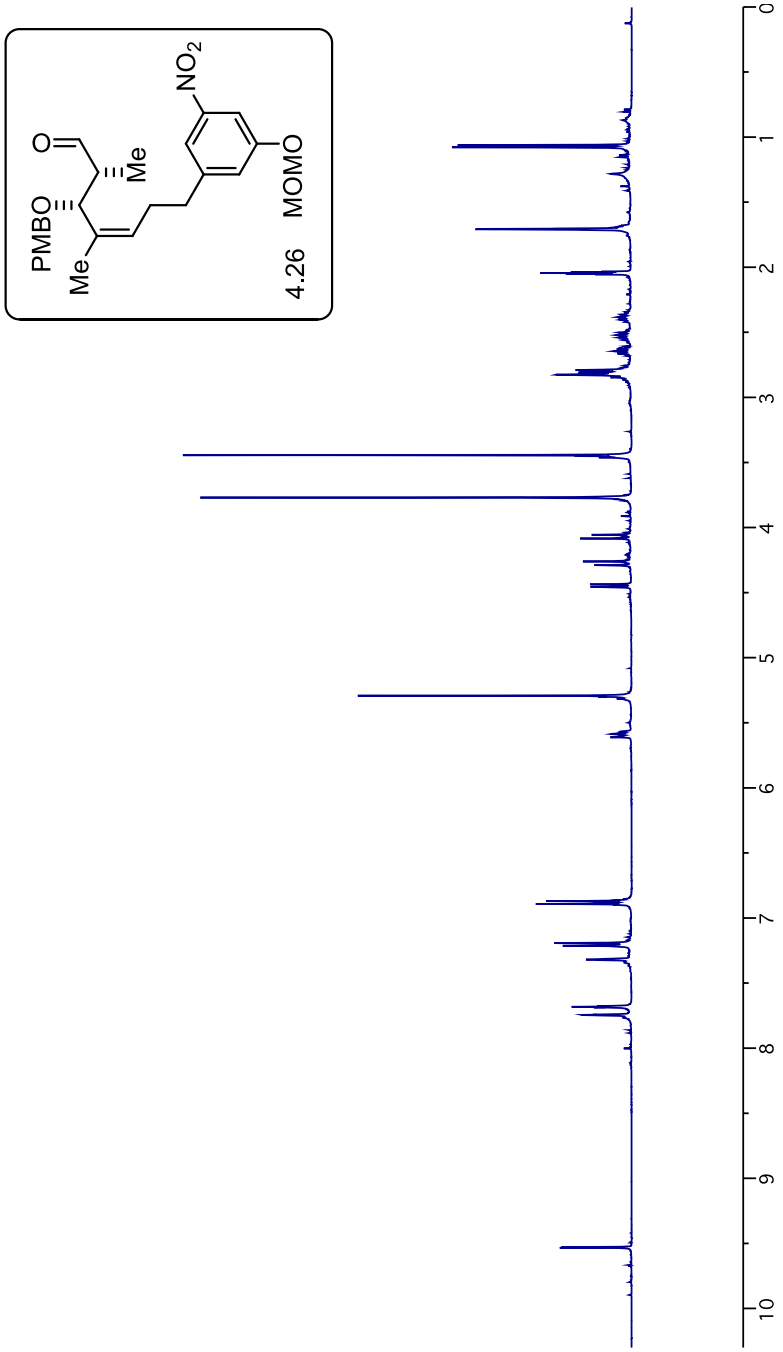


Figure 4.18 ^{1}H NMR spectrum of compound **4.26**

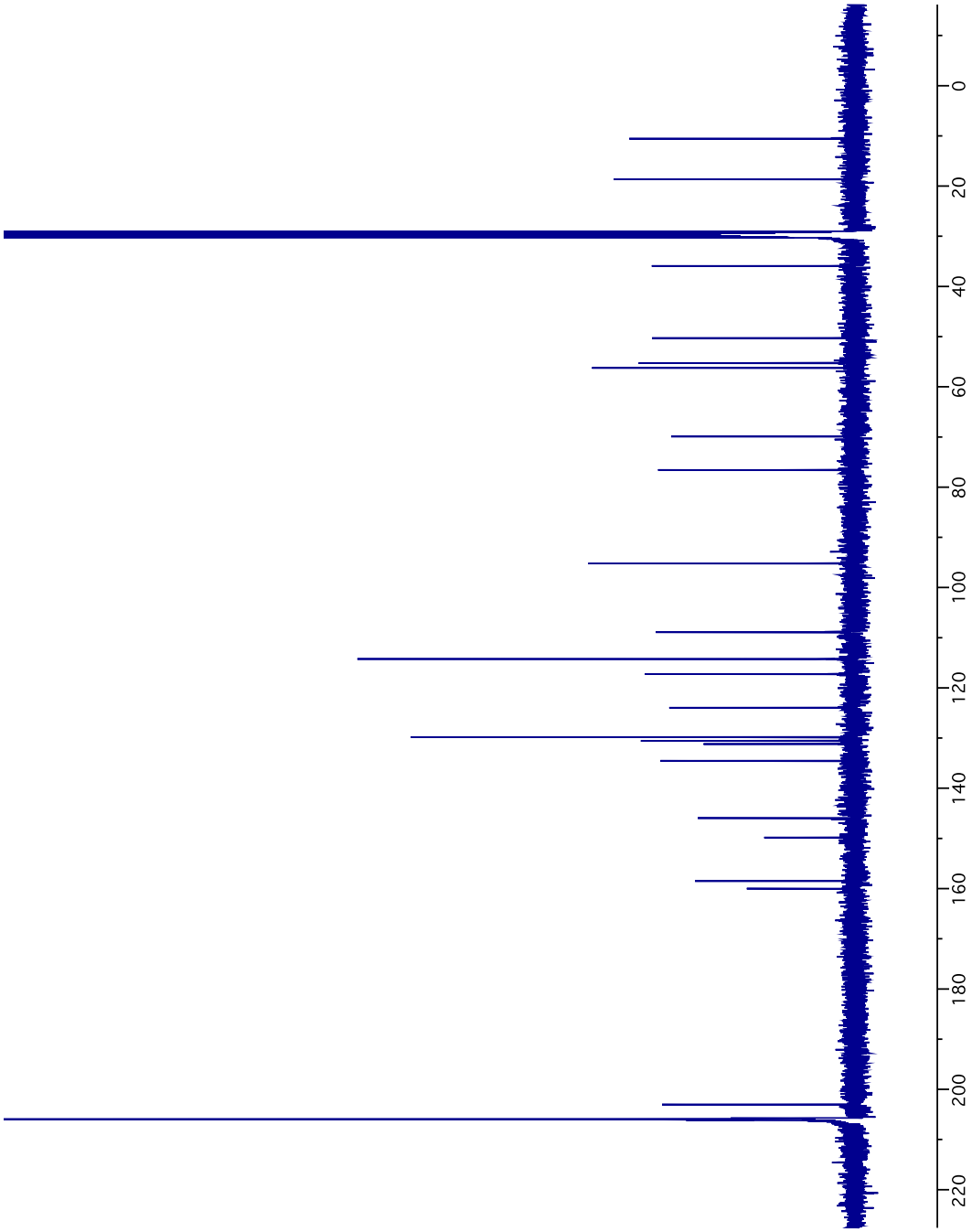


Figure 4.19 ^{13}C NMR spectrum of compound **4.26**

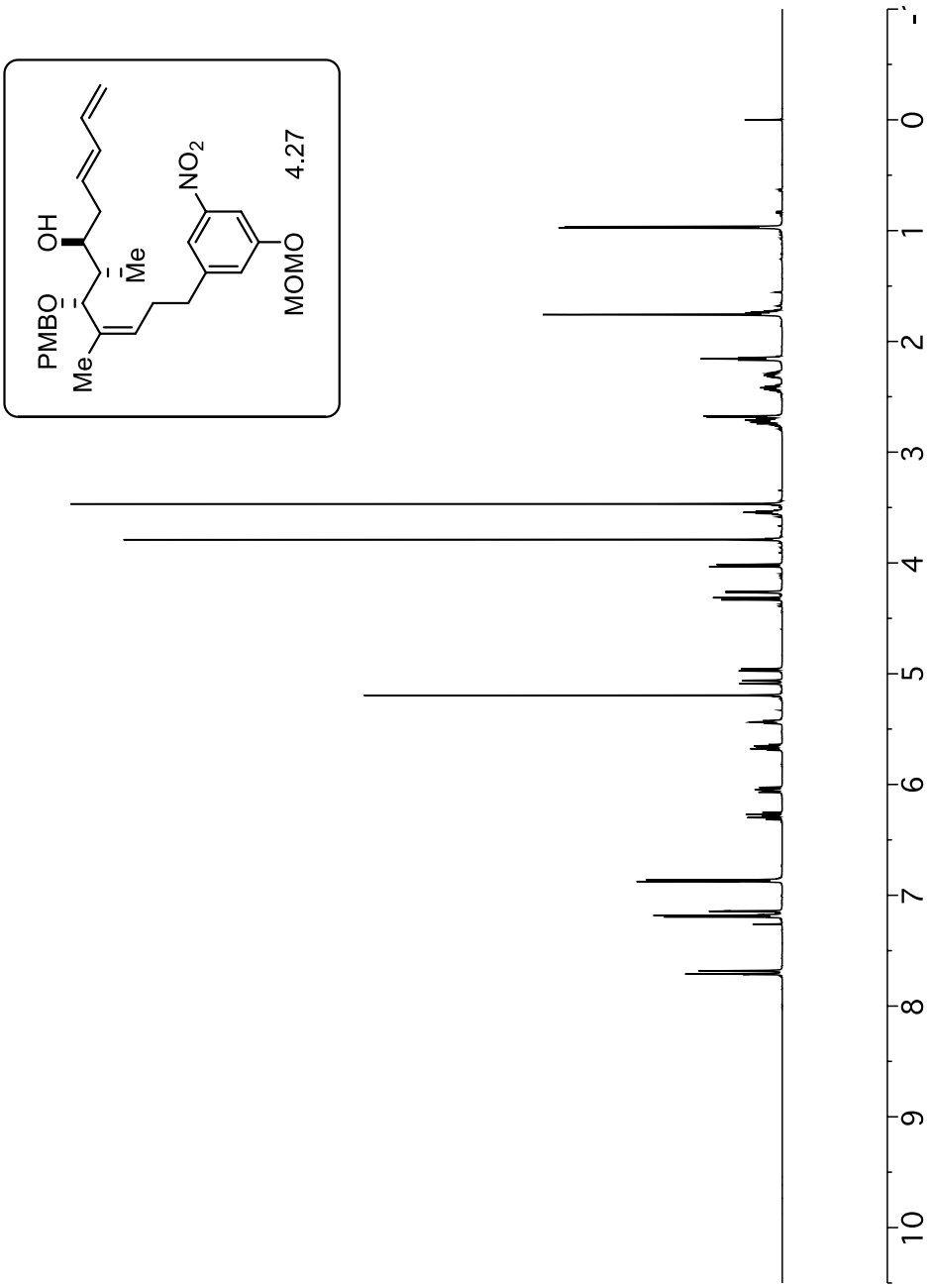


Figure 4.20 ^{1}H NMR spectrum of compound **4.27**

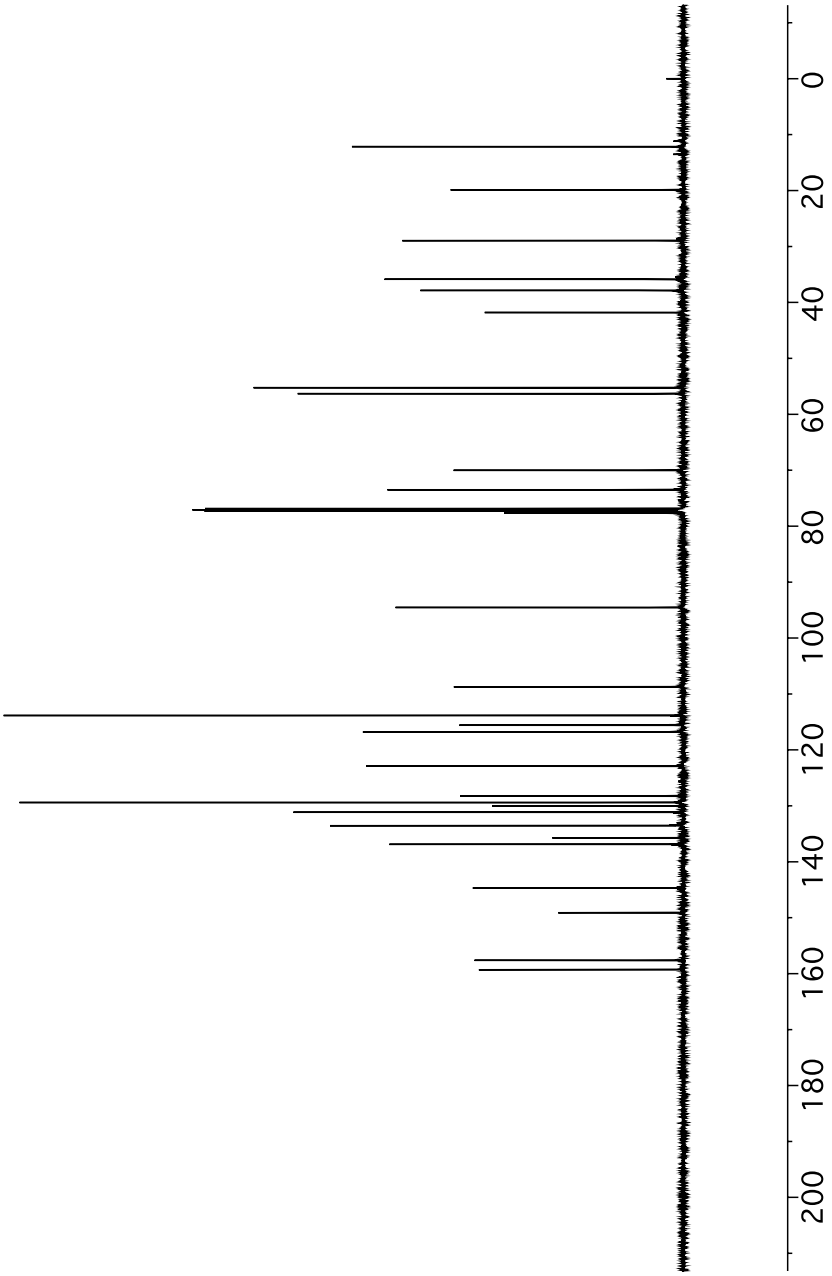


Figure 4.21 ^{13}C NMR spectrum of compound **4.27**

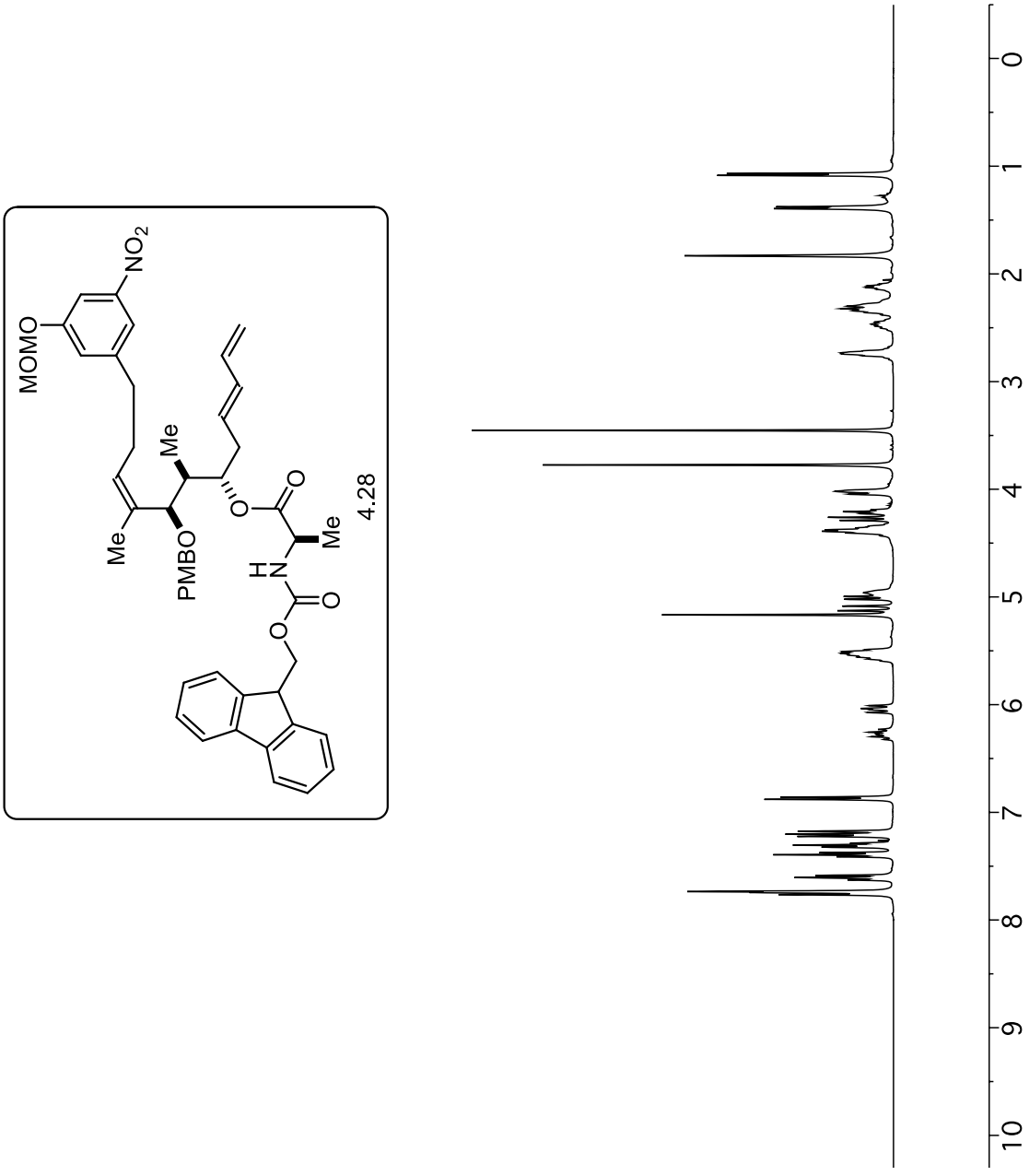


Figure 4.22 ^{1}H NMR spectrum of compound **4.28**

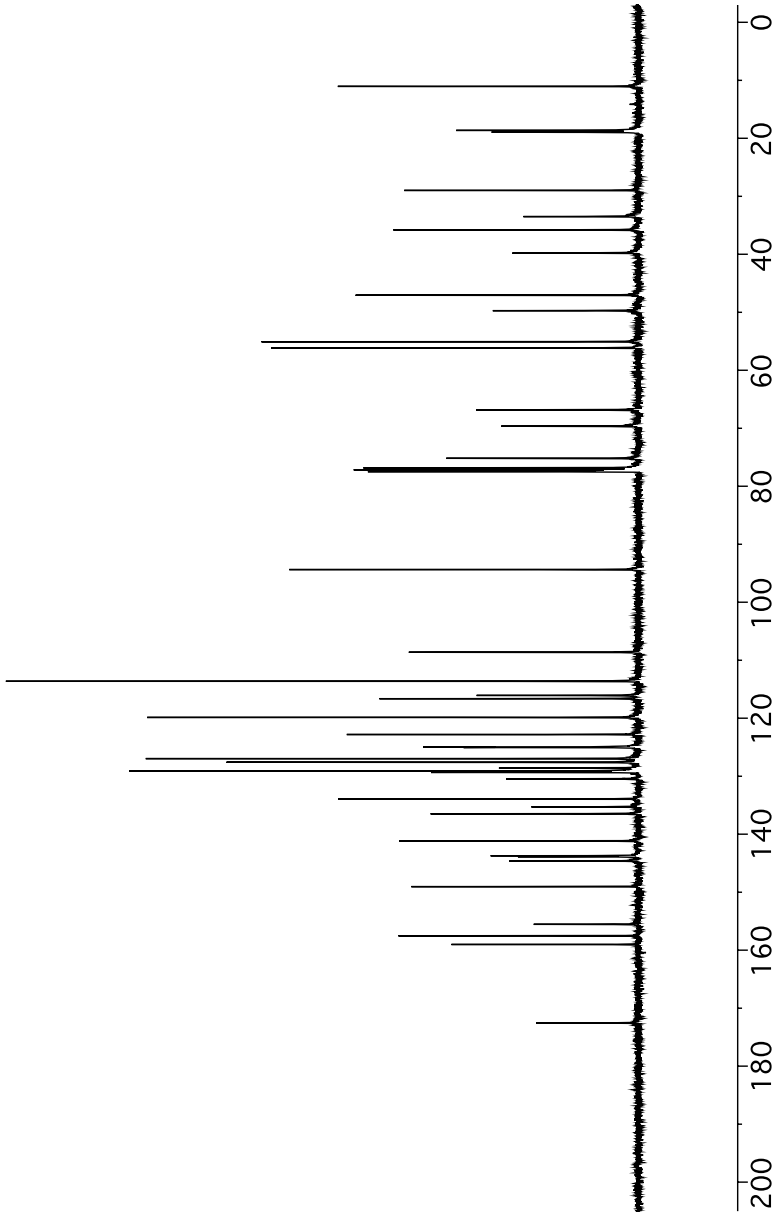


Figure 4.23 ^{13}C NMR spectrum of compound **4.28**

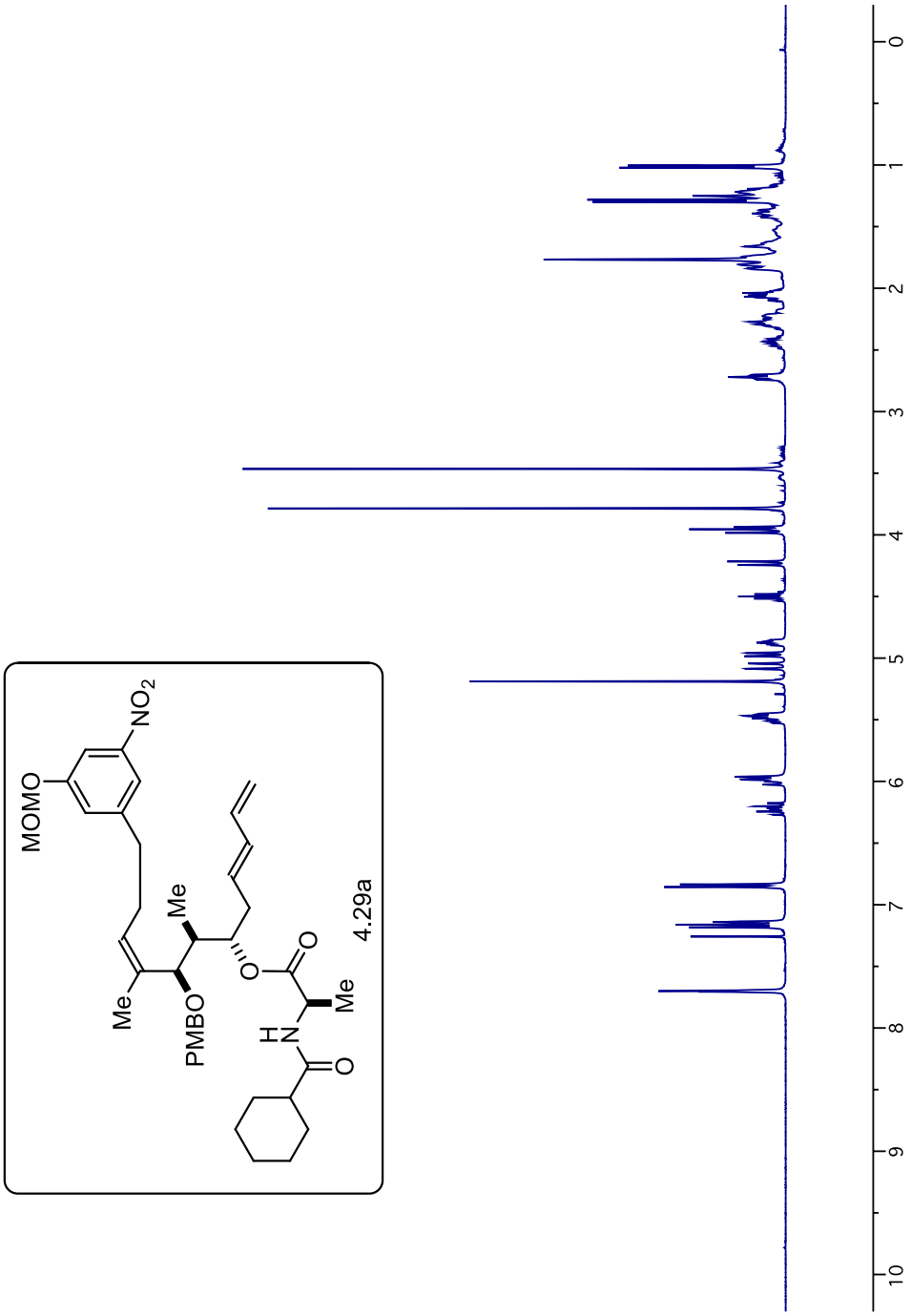


Figure 4.24 ^{1}H NMR spectrum of compound **4.29a**

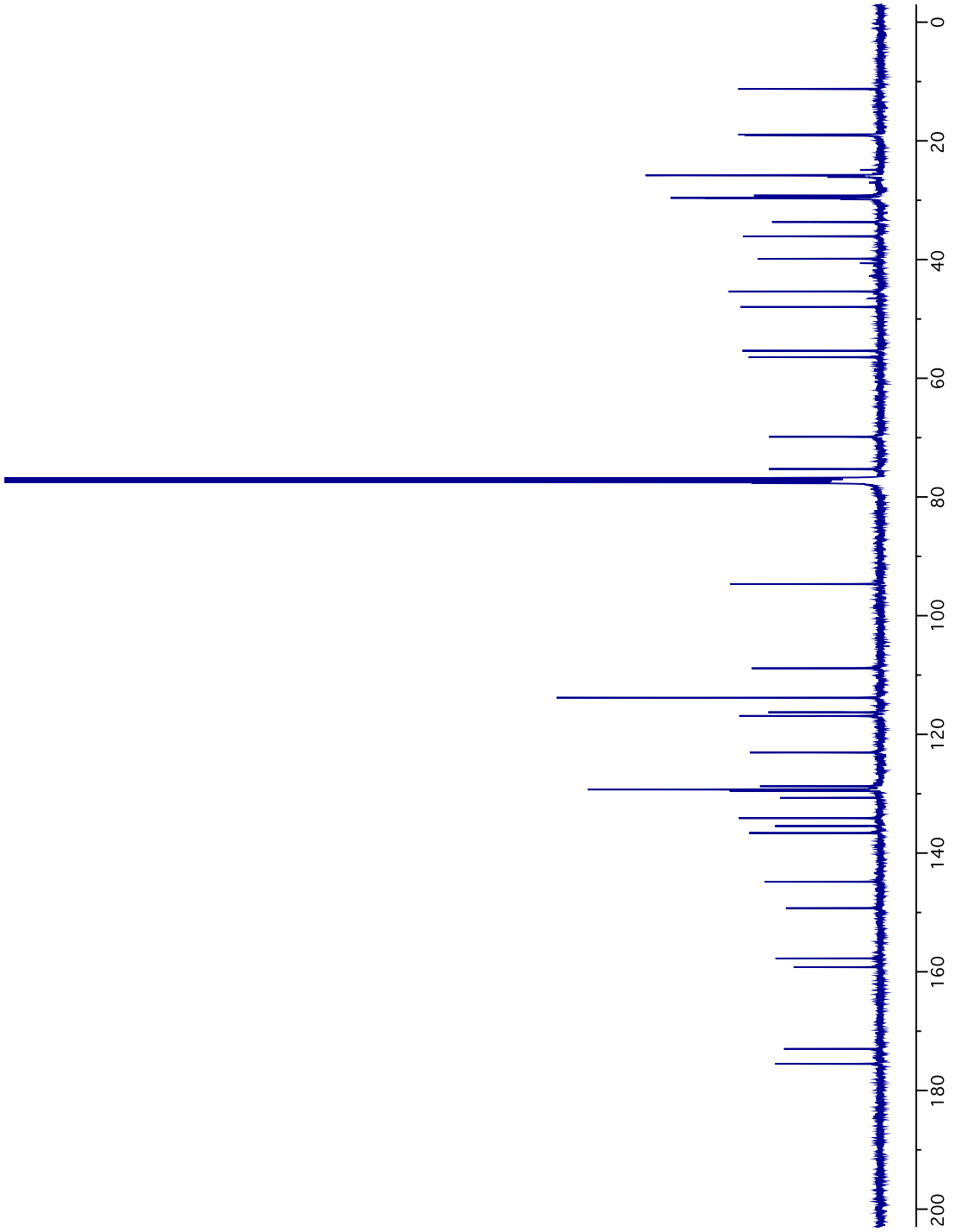


Figure 4.25 ^{13}C NMR spectrum of compound **4.29a**

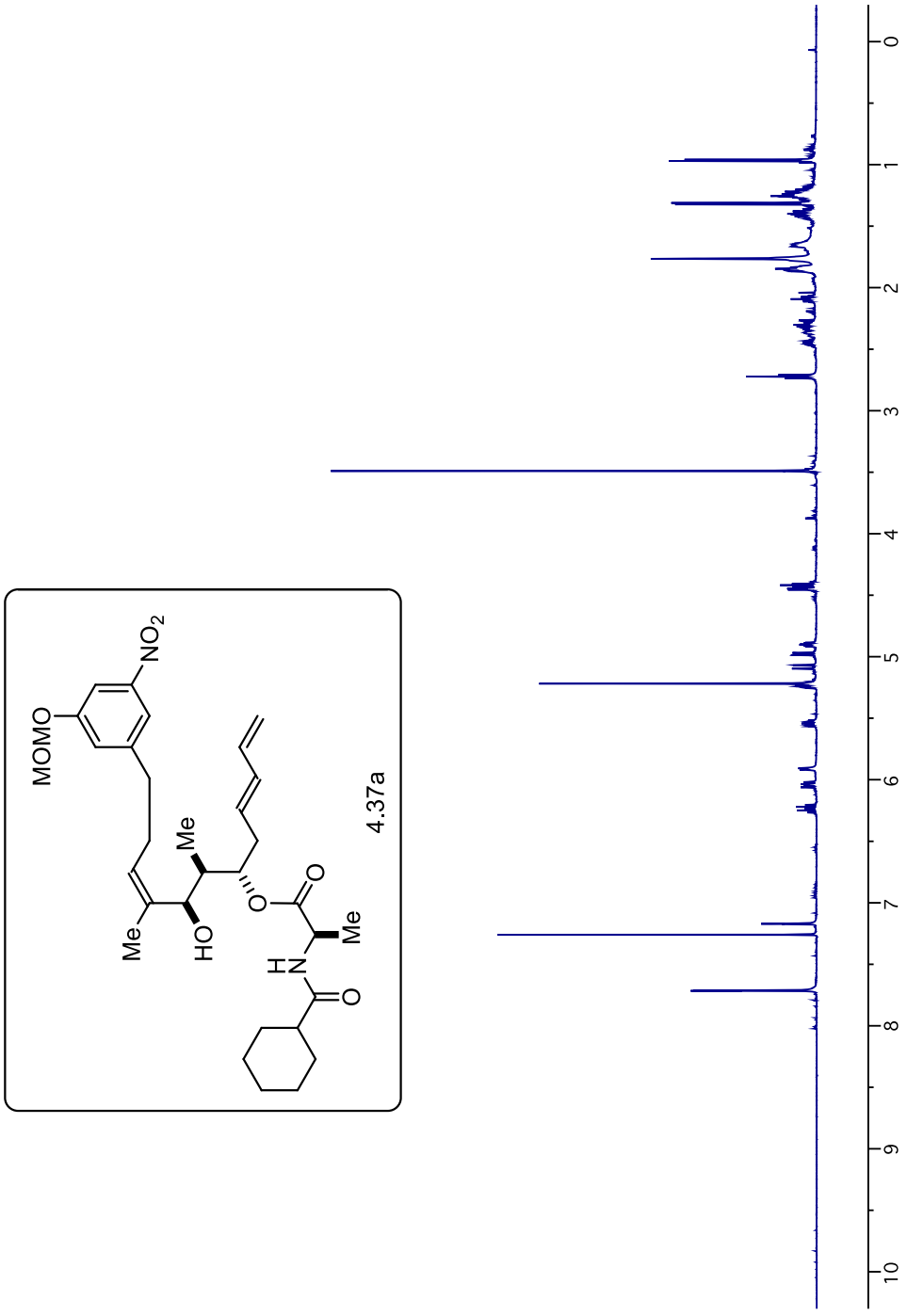


Figure 4.26 ^{1}H NMR spectrum of compound **4.37a**

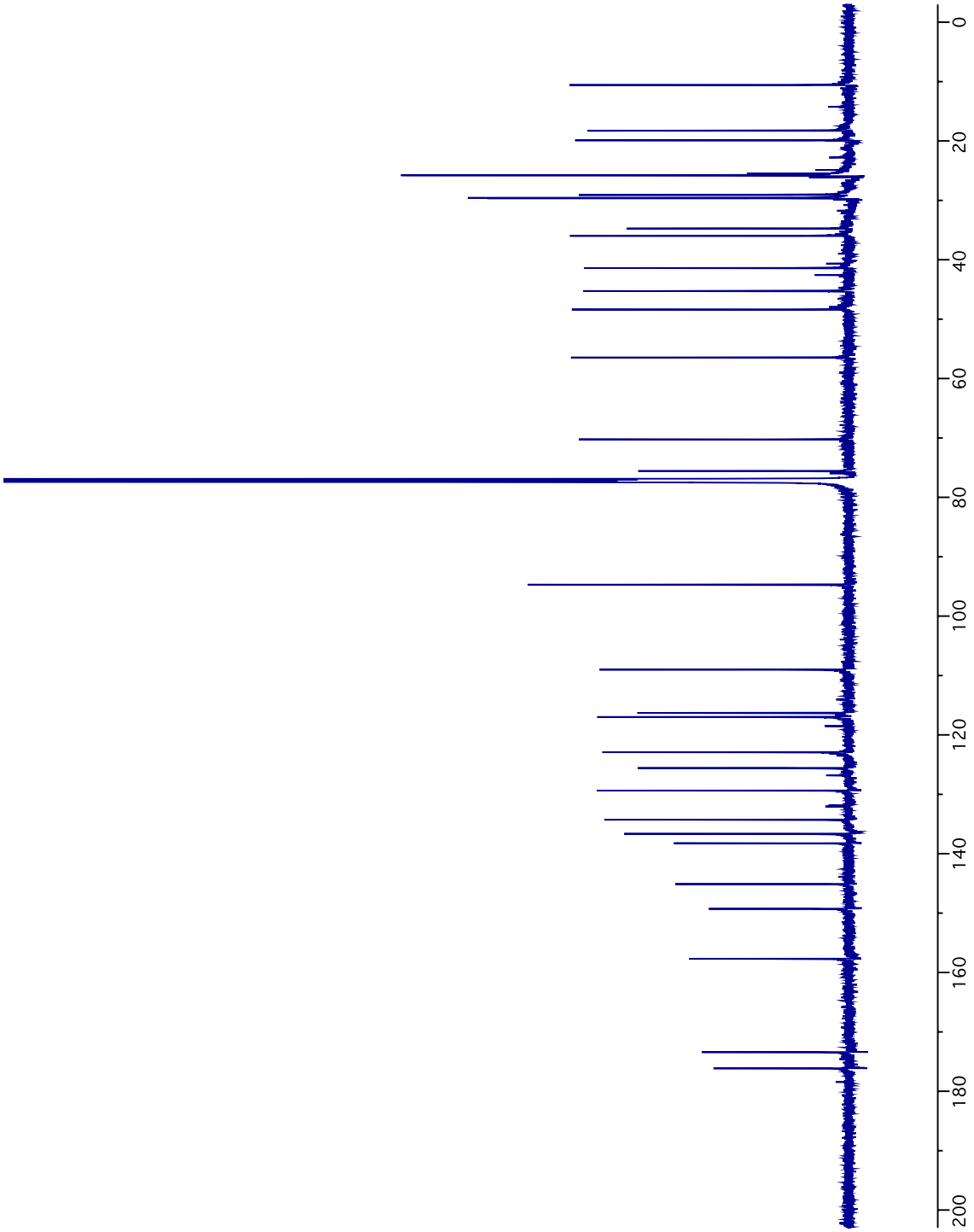


Figure 4.27 ^{13}C NMR spectrum of compound **4.37a**

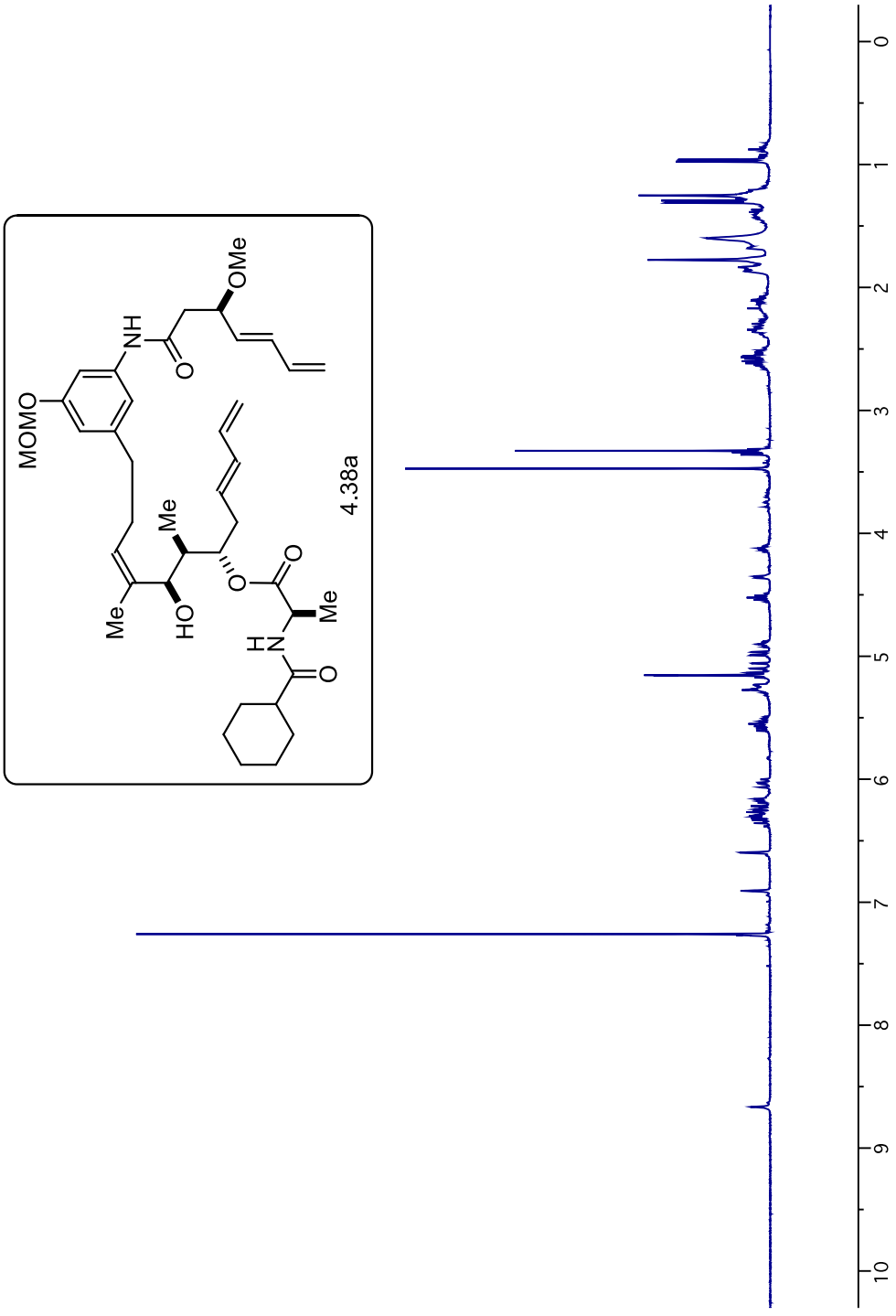


Figure 4.28 ^{1}H NMR spectrum of compound **4.38a**

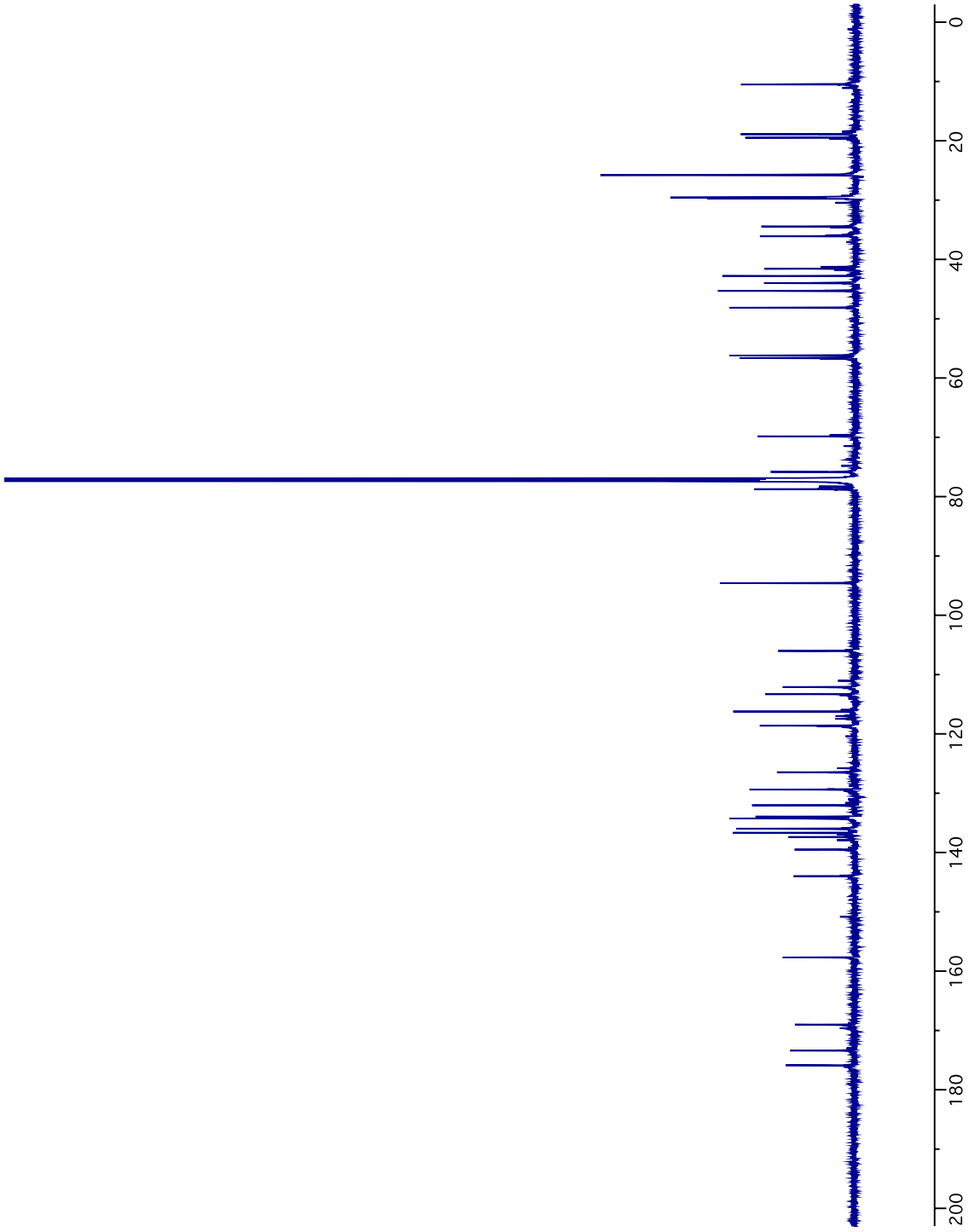


Figure 4.29 ^{13}C NMR spectrum of compound **4.38a**

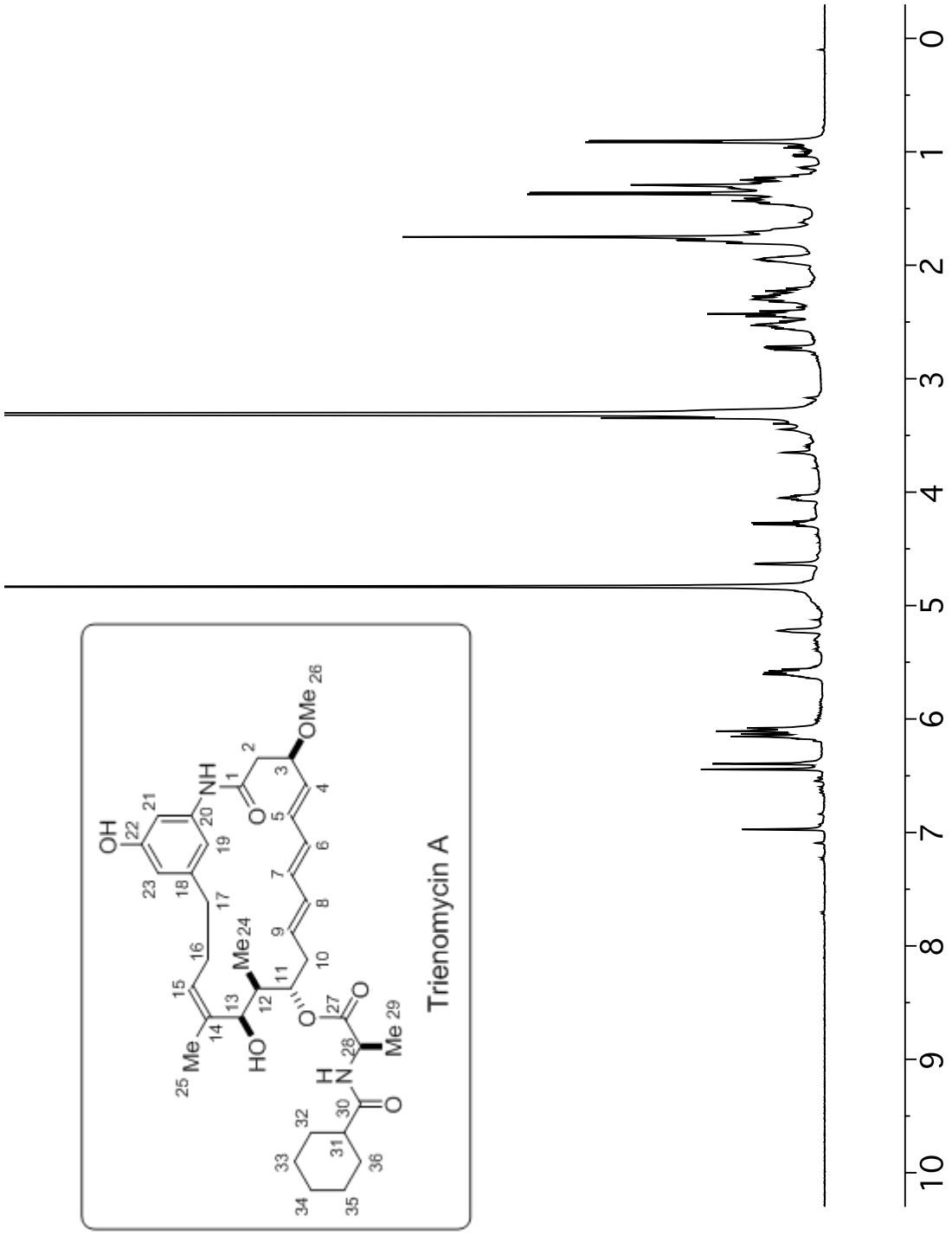


Figure 4.30 ^{1}H NMR spectrum of trienomycin A (**1.1a**)

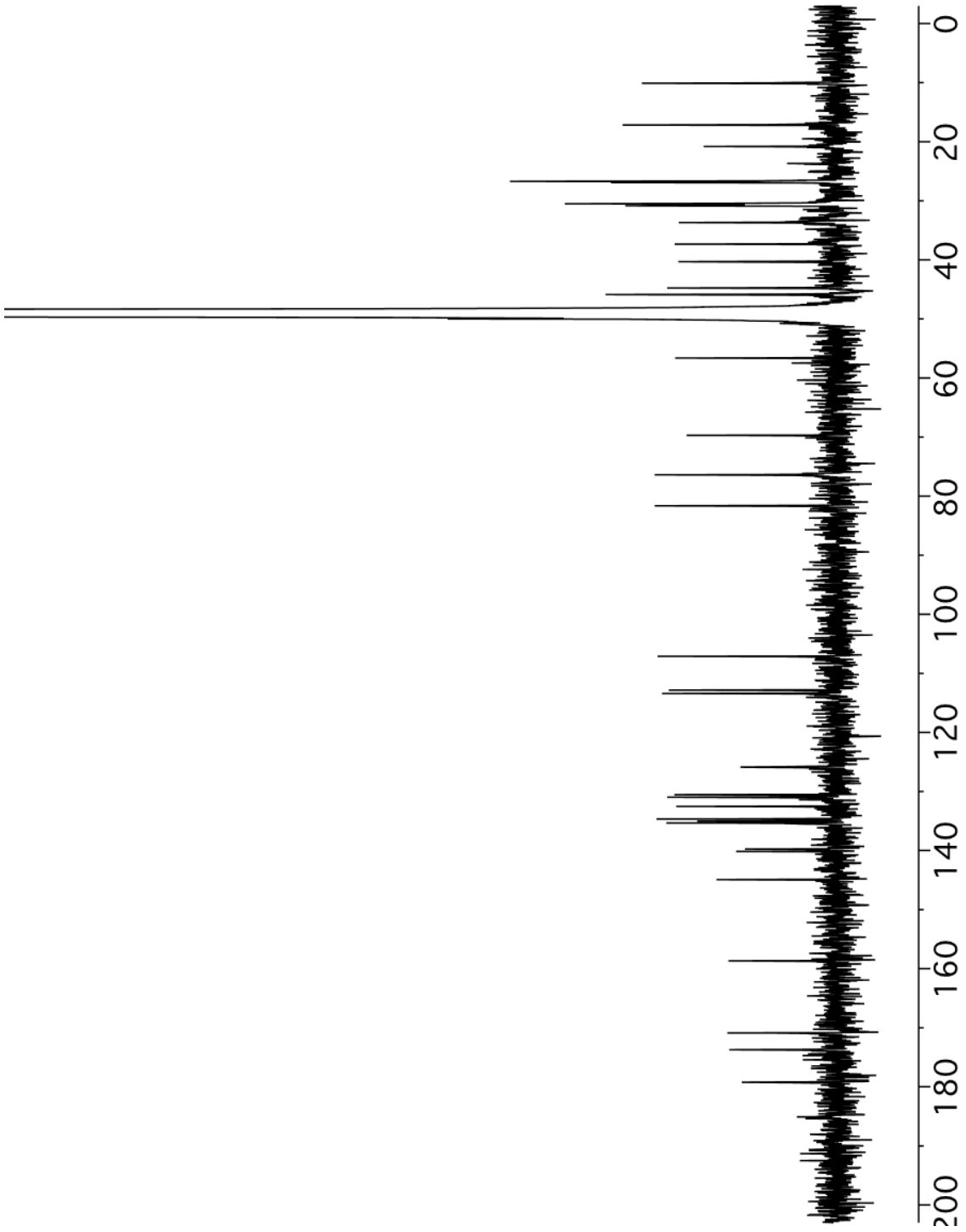


Figure 4.31 ^{13}C NMR spectrum of trienomycin A (**1.1a**)

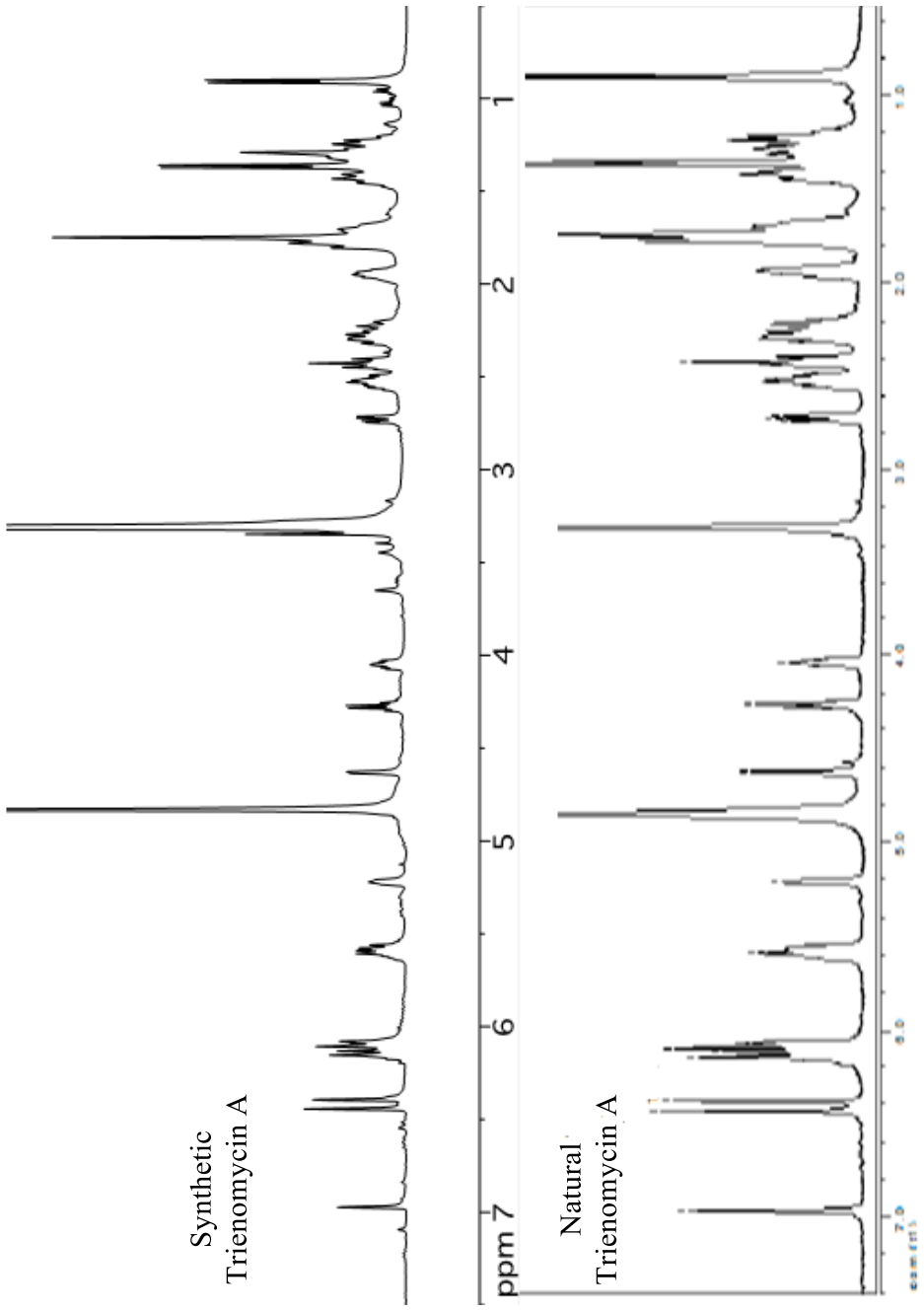


Figure 4.32 Comparison of ^{1}H NMR spectra of natural[145] and synthetic trienomycin A

No.	Natural[145] (δ)	Synthetic (δ)	Δ (δ)
1	170.9	170.9	0.0
2	44.8	44.8	0.0
3	81.6	81.6	0.0
4	132.5	132.5	0.0
5	135.3	135.3	0.0
6	131.0	131.0	0.0
7	135.0	135.0	0.0
8	134.7	134.7	0.0
9	130.6	130.6	0.0
10	33.7	33.7	0.0
11	76.4	76.4	0.0
12	40.4	40.3	0.1
13	69.7	69.7	0.0
14	139.8	139.8	0.0
15	125.9	125.9	0.0
16	30.9	30.9	0.0
17	37.4	37.4	0.0
18	140.2	140.2	0.0
19	112.9	112.8	0.1
20	145.0	145.0	0.0
21	107.2	107.1	0.1
22	158.7	158.7	0.0
23	113.5	113.4	0.1
24	10.1	10.1	0.0
25	20.8	20.8	0.0
26	56.7	56.7	0.0
27	173.8	173.7	0.1
28	50.0	50.0	0.0
29	17.2	17.2	0.0
30	179.2	179.2	0.0
31	45.9	45.9	0.0
32	30.6	30.6	0.0
33	26.7	26.7	0.0
34	26.9	26.9	0.0
35	26.7	26.7	0.0
36	30.5	30.5	0.0

Table 4.2 Comparison of ^{13}C NMR data of natural[145] and synthetic trienomycin A

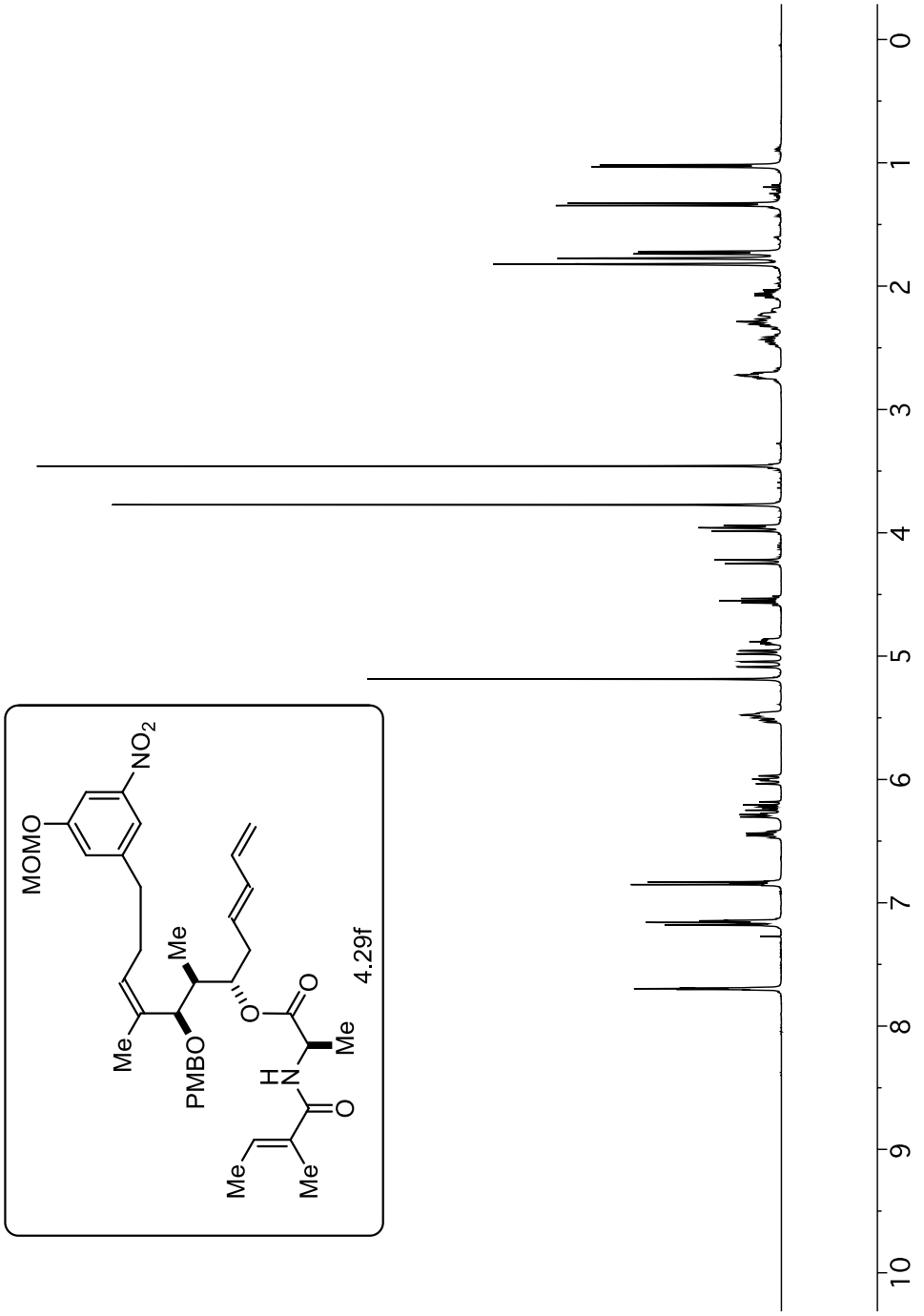


Figure 4.33 ^{1}H NMR spectrum of compound **4.29f**

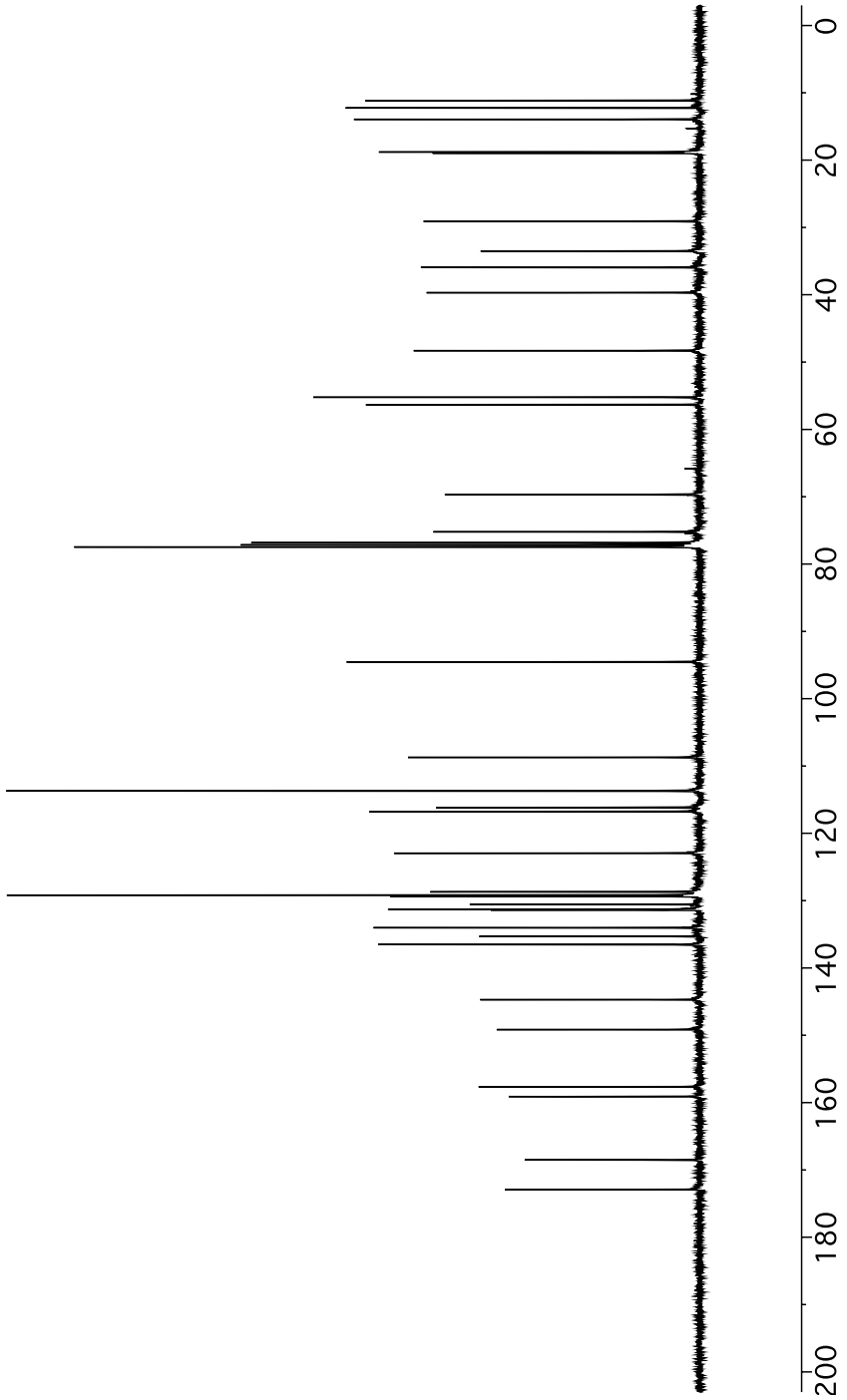


Figure 4.34 ^{13}C NMR spectrum of compound **4.29f**

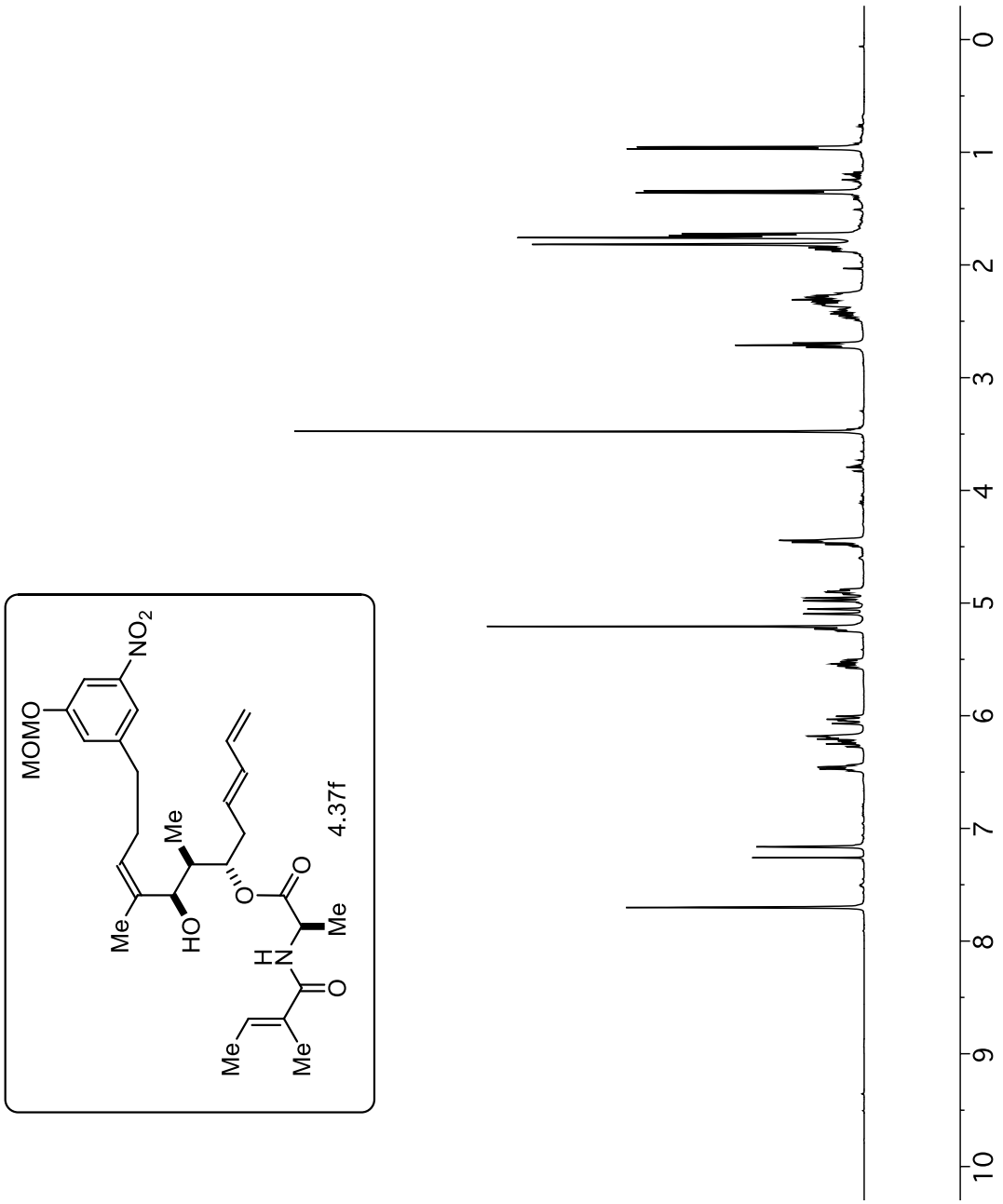


Figure 4.35 ^{1}H NMR spectrum of compound **4.37f**

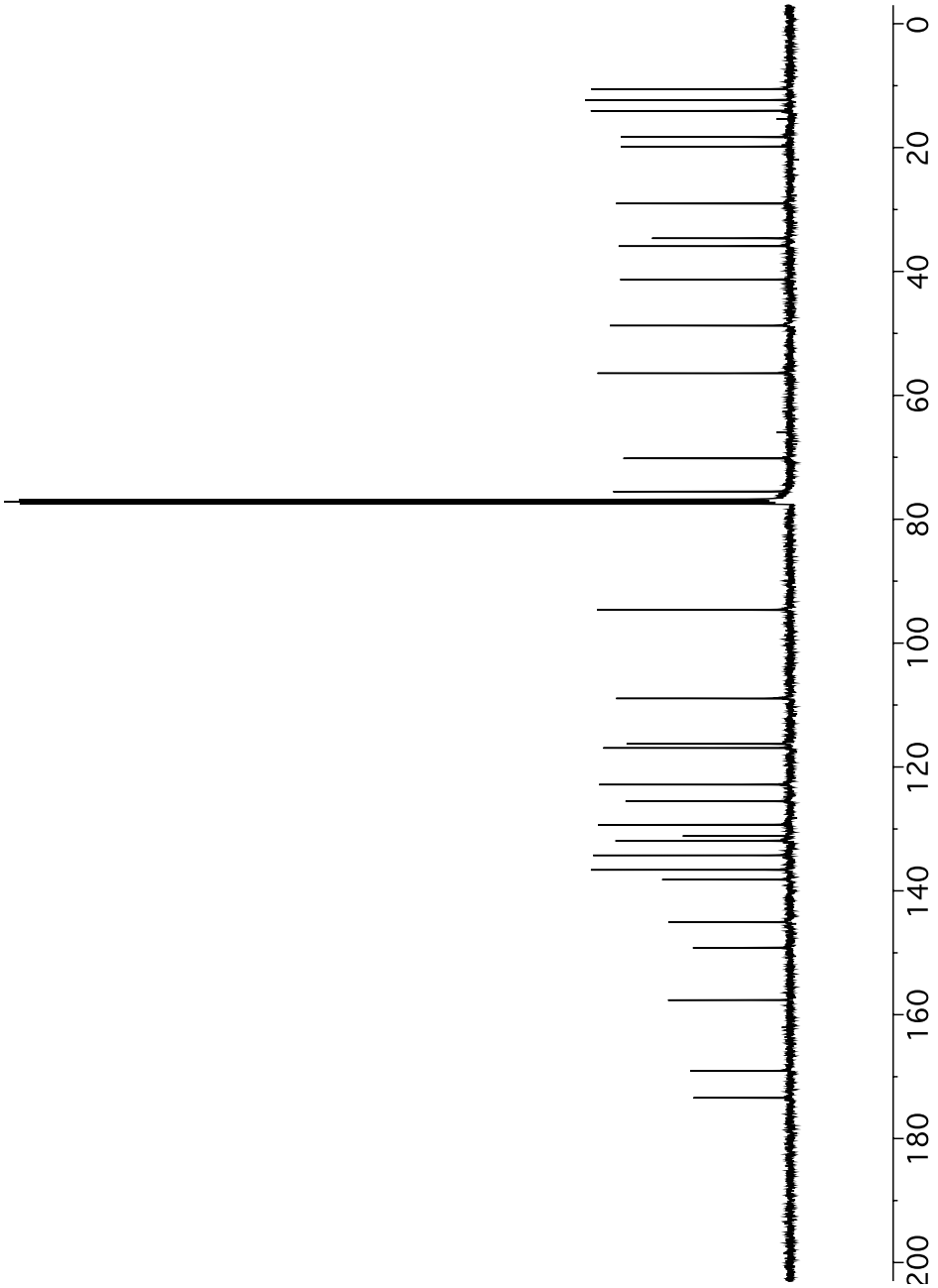


Figure 4.36 ^{13}C NMR spectrum of compound **4.37f**

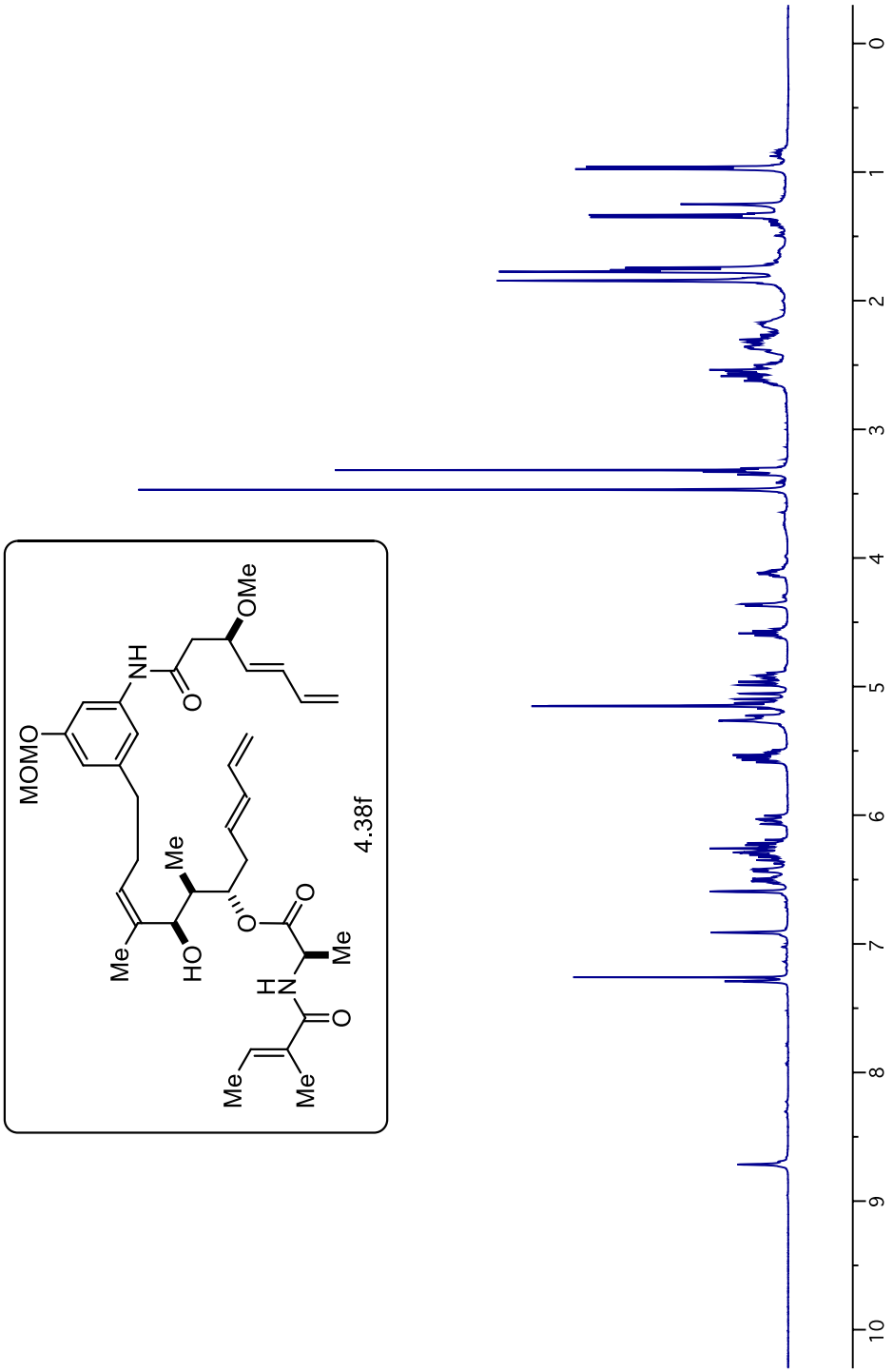


Figure 4.37 ^{1}H NMR spectrum of compound **4.38f**

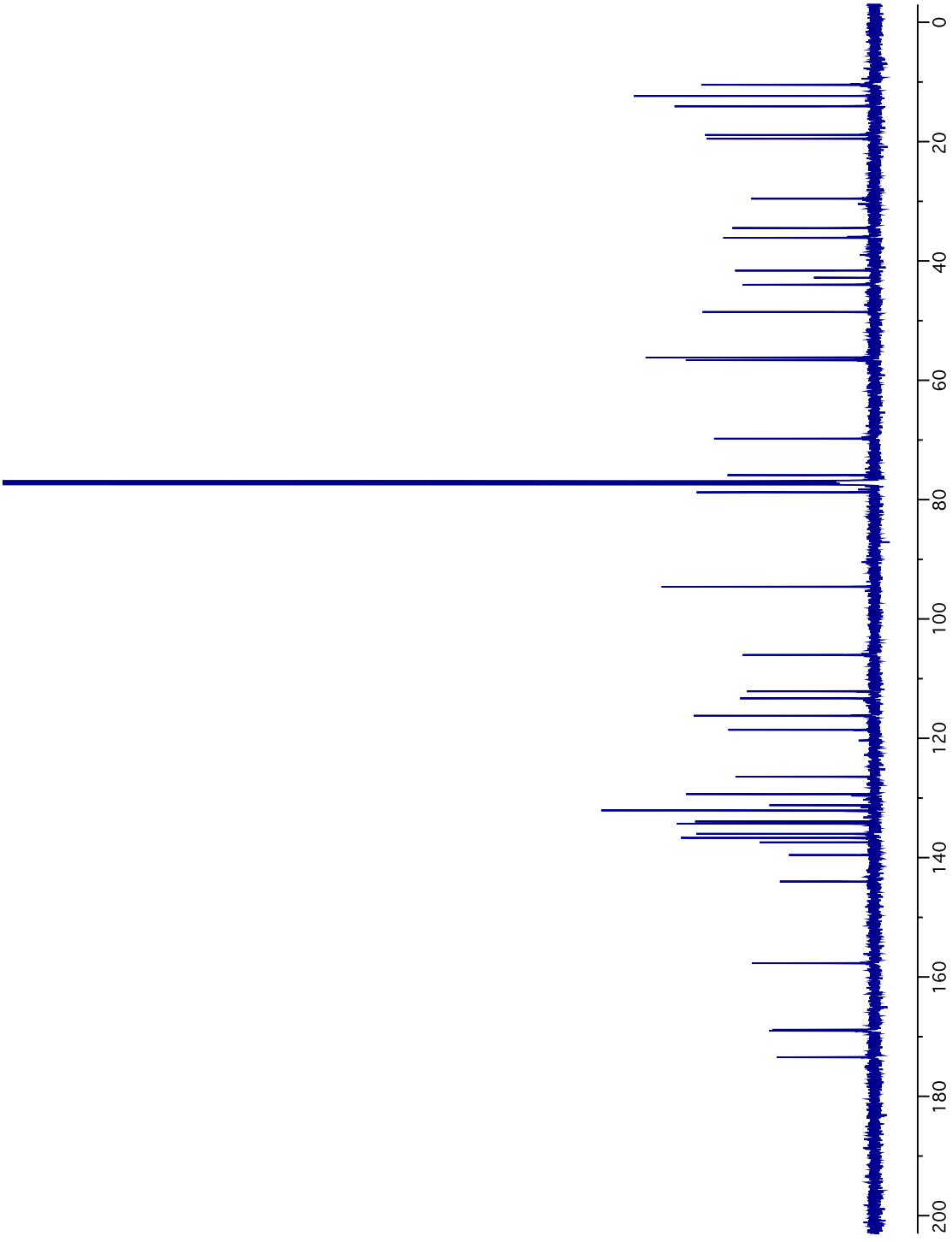


Figure 4.38 ^{13}C NMR spectrum of compound **4.38f**

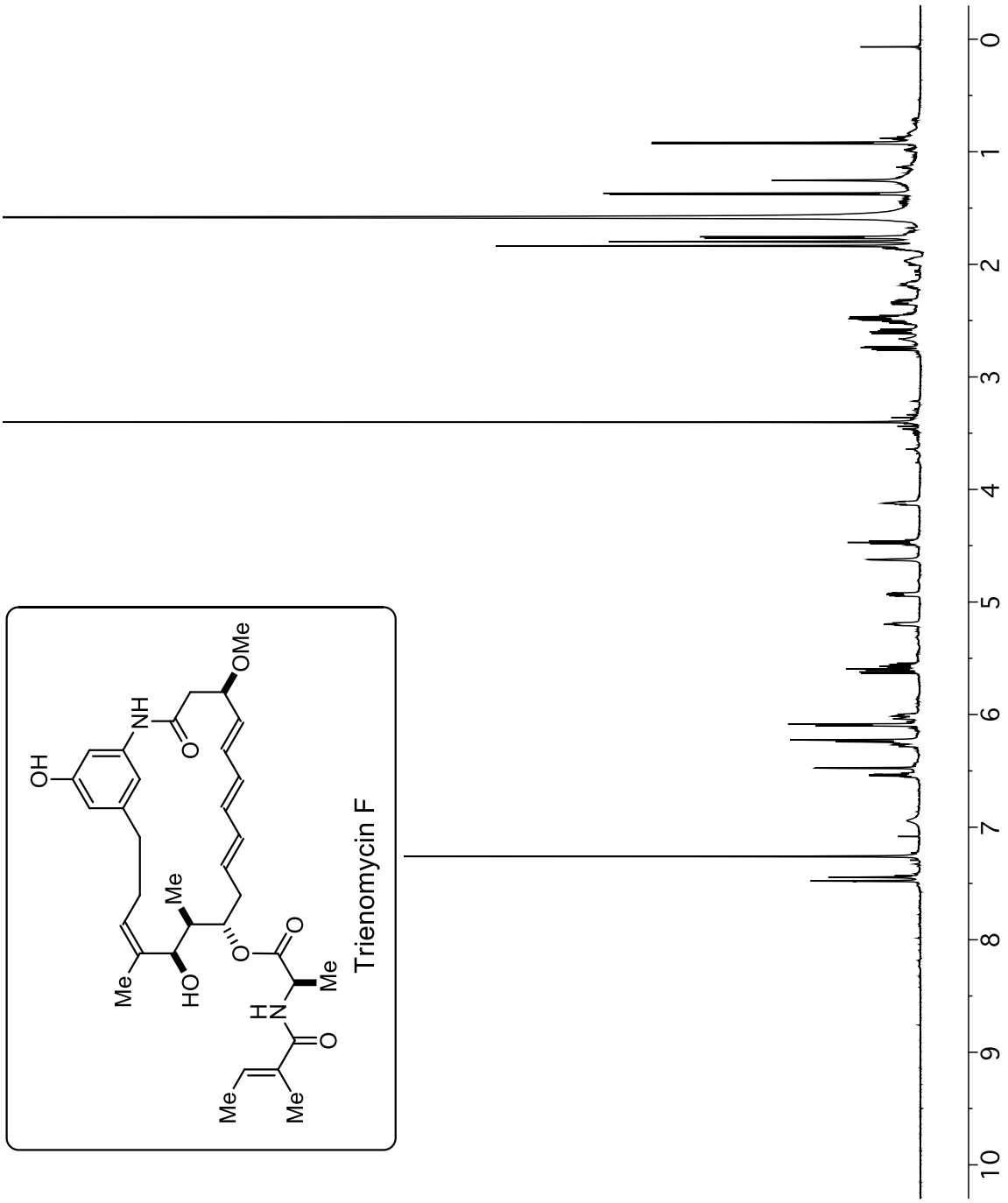


Figure 4.39 ^{1}H NMR spectrum of trienomycin F (**1.1f**)

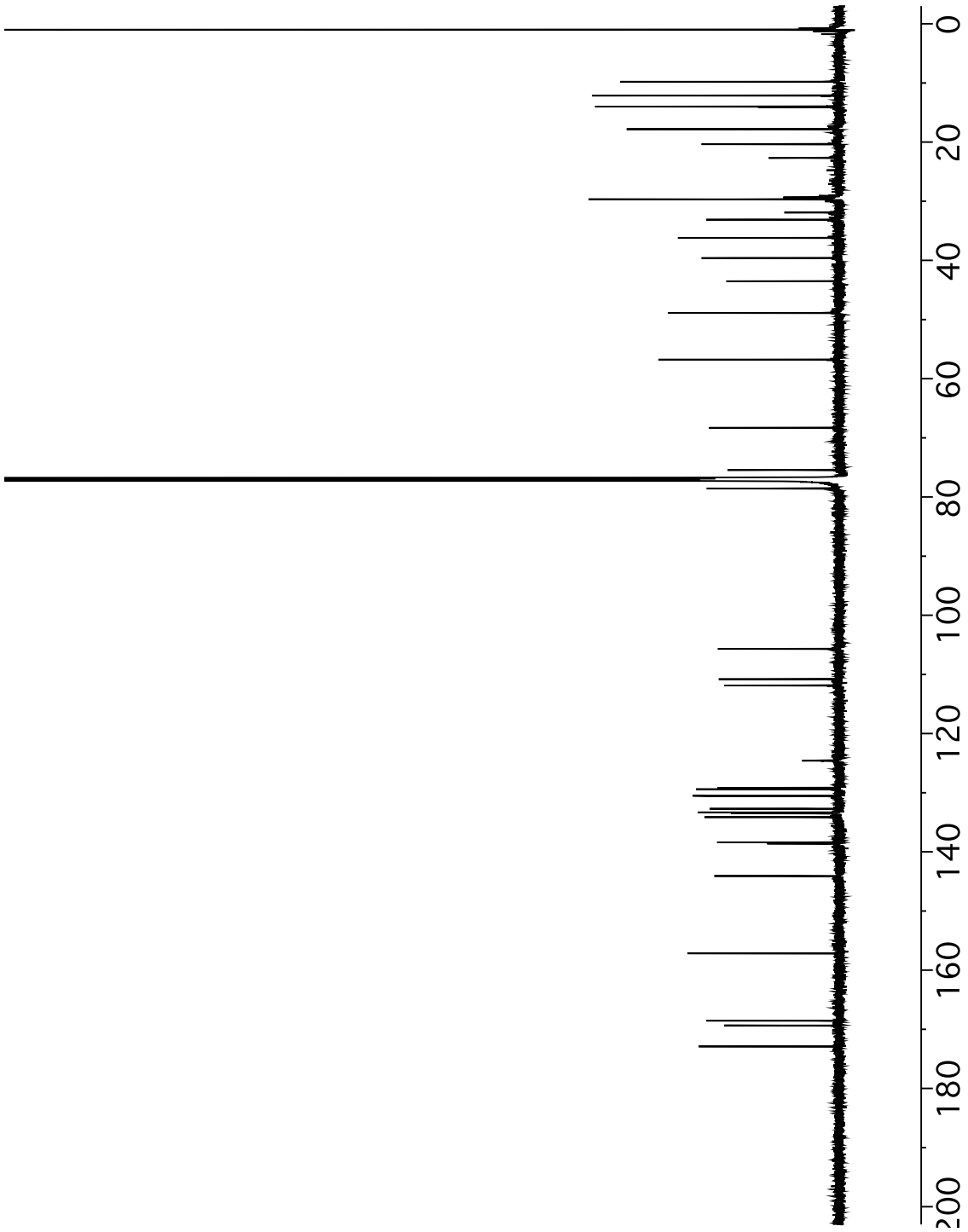


Figure 4.40 ^{13}C NMR spectrum of trienomycin F (**1.1f**)

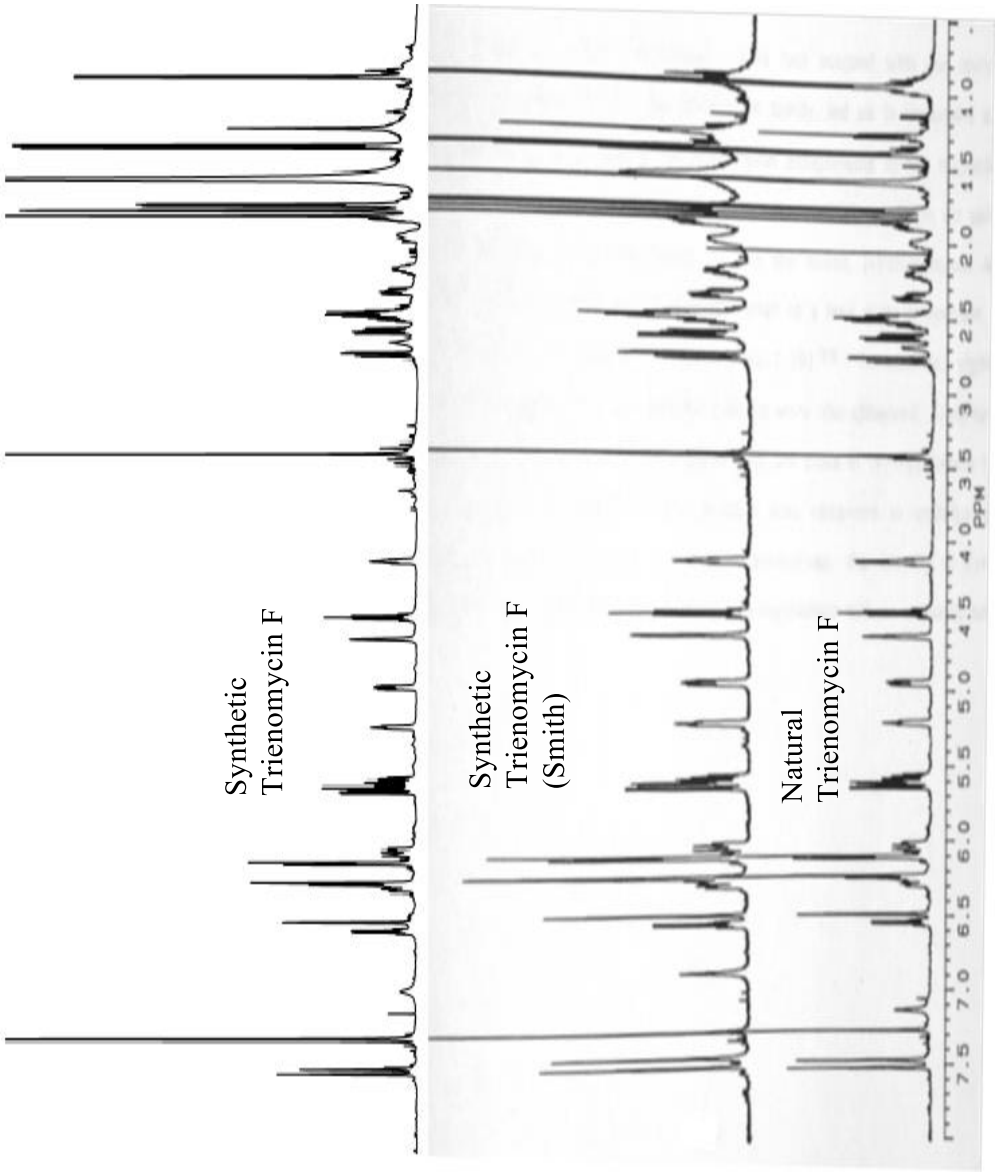
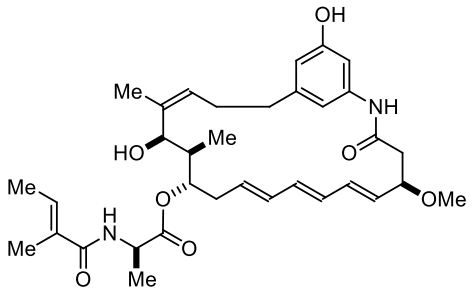


Figure 4.41 Comparison of ^{1}H NMR spectra of natural and synthetic trienomycin F



Natural (δ)	Synthetic (δ)	Δ (δ)
172.9	172.9	0.0
169.3	169.3	0.0
168.4	168.5	0.1
157.1	157.1	0.0
144.1	144.0	0.1
138.6	138.6	0.0
138.4	138.3	0.1
134.1	134.1	0.0
133.4	133.4	0.0
133.3	133.3	0.0
132.7	132.7	0.0
130.6	130.6	0.0
130.5	130.5	0.0
129.3	129.4	0.1
129.2	129.1	0.1
124.5	124.5	0.0
111.8	111.8	0.0
110.8	110.8	0.0
105.6	105.6	0.0
78.5	78.5	0.0
75.4	75.4	0.0
68.3	68.4	0.1
56.8	56.8	0.0
48.8	48.8	0.0
43.5	43.5	0.0
39.6	39.6	0.0
36.1	36.2	0.1
33.1	33.1	0.0
29.7	29.6	0.1
20.3	20.3	0.0
17.8	17.8	0.0
14.0	14.0	0.0
12.1	12.1	0.0
9.7	9.8	0.1

Table 4.3 Comparison of ^{13}C NMR data of natural[25] and synthetic trienomycin F

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